Library
OF THE
New York State Veterinary College

Cornell University Library
RC 636.W25

Bedside hæmatology; an introduction to th

3 1924 000 295 281 vet

Cornell University Library

The original of this book is in
the Cornell University Library.

There are no known copyright restrictions in
the United States on the use of the text.

http://www.archive.org/details/cu31924000295281

BEDSIDE HÆMATOLOGY

AN INTRODUCTION TO THE CLINICAL STUDY OF THE SO-CALLED BLOOD DISEASES AND OF ALLIED DISORDERS

BY

GORDON R. WARD, M. D. (Lond.)

FELLOW OF THE ROYAL SOCIETY OF MEDICINE, MEDICAL SOCIETY OF LONDON, ETC.

ILLUSTRATED

PHILADELPHIA AND LONDON
W. B. SAUNDERS COMPANY
1914

NEW YORK STATE
VETERINARY COLLEGE
LIBRARY

NYS 12

Copyright, 1914, by W. B. Saunders Company

RC
636
W25
storage

PRINTED IN AMERICA

PRESS OF
W. B. SAUNDERS COMPANY
PHILADELPHIA

DEDICATED
TO
RICHARD GRAINGER HEBB, M.A., M.D., F.R.C.P.
BY
HIS PUPIL
IN GRATEFUL RECOGNITION OF HIS
TEACHING, HIS CRITICISMS AND
HIS MANY KINDNESSES

PREFACE

THIS volume is primarily concerned with that clinical study of the so-called blood diseases which has been so much overshadowed by exclusively pathological investigation. It is secondly concerned with the classification of blood diseases, inasmuch as this is a necessary preliminary to any understanding of their nature.

The author wishes to express his gratitude to those who have kindly lent him illustrations and, in particular, to Dr. O. R. M. Kelly for revising a great part of his manuscript.

GORDON R. WARD.

LONDON, ENGLAND,
April, 1914.

CONTENTS

CHAPTER I

PAGE
GENERAL REMARKS AND CLASSIFICATION 17

CHAPTER II

THE BLOOD-FORMING ORGANS 26
The Marrow 27
The Lymphoid Tissues 28
The Spleen 29
The Liver 30
The Blood and its Cells 31

CHAPTER III

METHOD OF MAKING A BLOOD EXAMINATION 40

CHAPTER IV

GENERALISED AFFECTIONS OF BLOOD-FORMING TISSUES 49
Lymphæmia 51

CHAPTER V

CHLOROMA AND MYELÆMIA 88
Chloroma 88
Myelæmia 89

CHAPTER VI

HODGKIN'S DISEASE AND GAUCHER SPLENOMEGALY 110
Hodgkin's Disease 110
Gaucher Splenomegaly 130

CHAPTER VII

LOCALISED AFFECTIONS OF BLOOD-FORMING TISSUES 133
Lymphoma 134
Multiple Myeloma 134
Splenic Anæmia of Adults 137
Lymphatism 148

CHAPTER VIII

PAGE
INCREASED RED-CELL FORMATION 154
Erythræmia 155
Secondary or Symptomatic Polycythæmia 175
Blood Crisis 183
Post-hæmorrhagic Anæmia 185

CHAPTER IX

ACUTE APLASTIC ANÆMIA 186
Congenital Anæmia. 188

CHAPTER X

ATROPHIC ANÆMIAS AND OTHER SECONDARY ANÆMIAS 191
Splenic Anæmia of Infants 214
Senile Anæmia 220

CHAPTER XI

CHOLÆMIA 221

CHAPTER XII

ADDISONIAN ANÆMIA 235
Other Hæmolytic Anæmias 261

CHAPTER XIII

HÆMOCHROMATOSIS, HÆMATOPORPHYRINURIA, HÆMOGLOBINURIA, ETC. . 262
Hæmochromatosis 262
Hæmatoporphyrinuria 264
Hæmoglobinuria 267
Intravascular Cytophagocytosis 276

CHAPTER XIV

PARASITIC DISEASES OF THE CIRCULATING RED CELLS 278

CHAPTER XV

CYANOSIS 279
Carboxyhæmoglobinæmia 283
Sulph-hæmoglobinæmia 292
Infective Methæmoglobinæmia. 298

CHAPTER XVI

LEUCOCYTOSIS 302
Polymorph Leucocytoses 302
Eosinophil Leucocytosis or Eosinophilia 303

LEUCOCYTOSIS (*continued*)

PAGE
Lymphocytosis 304
Mixed Leucocytosis 305
Leucopenia 305

CHAPTER XVII

CHLOROSIS 306

CHAPTER XVIII

HÆMOPHILIA 323
The Hæmorrhagic Disease of the New Born or Hæmophilia Neonatorum 329

CHAPTER XIX

PURPURA 331
Purpura Hæmorrhagica 332

CHAPTER XX

LEUKANÆMIA 333

CHAPTER XXI

THE BLOOD IN SURGICAL DIAGNOSIS 334

CHAPTER XXII

METHODS OF TREATMENT 338
Medical Treatment 338
Transfusion 343
The Employment of x-Rays 345
The Administration of Arsenic 347
The Administration of Iron 349

CHAPTER XXIII

THE BLOOD IN VARIOUS DISEASES 356

INDEX 385

BEDSIDE HAEMATOLOGY

CHAPTER I

GENERAL REMARKS AND CLASSIFICATION

Most of the morbid processes designated "Blood Diseases" are not in reality diseases of the blood but of the blood-forming organs. It is not even the case that the changes in the blood-forming organs are necessarily reflected in the blood stream, although this is often so. In Hodgkin's disease, for instance, and in splenic anæmia of adults, there is no alteration in the blood in the early stages and even when this occurs it is of a sort that is shared by many other pathological conditions, in fact, is nothing more than a common type of secondary anæmia.

In other cases, *e.g.*, hæmophilia, it is only by comparatively recent refinements of technique that we have been able to demonstrate any alteration in the blood at all.

It is obvious from these and similar considerations that the mere name "Blood Diseases" will not afford us much assistance in arriving at a suitable limitation of the morbid processes to be dealt with in this volume but this limitation must be our first concern.

It might, at first sight, seem fairly easy to differentiate primary and secondary affections of the blood-forming organs. In practice it is extraordinarily difficult and weight must also be allowed to the fact that custom does not permit the exclusion of the secondary disorders from a book of this nature. This being the case we can base no limitation on this distinction.

After prolonged consideration of the possibilities and after almost giving up the idea of attempting a classification, the present writer feels that the diseases to be treated of must be chosen somewhat arbitrarily. It is therefore proposed to study a group which may be said to comprise disorders of the blood-forming organs, of the circulating blood, of blood formation and of blood destruction. It must even then be understood that infective disease of the blood-forming organs is excluded and also malignant disease in the usual conception of that term. It will further appear later that no adequate consideration of the parasitic diseases could suitably appear in this volume and, in consequence, these also must be excluded.

Passing on to the minuter details of classification we see at once that there are certain diseases which stand alone by virtue of the distribution of the characteristic lesions in all of the blood-forming organs, the marrow, the spleen, the lymph glands and the liver (which is only a blood-forming organ in fœtal and possibly very early extra-uterine life). Moreover the changes in question appear to be primary in each situation and to be the local expressions of a stimulus which has called them all into being. They are not of the nature of metastases. Finally not only do they invade the active blood-forming tissues but they also call into being blood-forming tissue wherever lymphoid cells are found. This includes the whole of the mesoblastic tissues.

These diseases may appropriately be grouped together as Generalised Affections of Blood-forming Tissues. They are the Leukæmias, Hodgkin's Disease and the Gaucher form of Splenomegaly.

It is just possible that Splenic Anæmia of Adults should be placed in the last group since the fibrotic changes commonly most marked in the spleen not infrequently extend to the liver and may perhaps involve also the lymph glands and marrow. Until further histological evidence is forthcoming it seems as well to keep it in the second group, viz., Local Affections of Blood-forming Tissues. It is here associated with certain primary diseases which are not generalised in the way just mentioned, viz., Multiple Myeloma and Lymphoma and with one secondary disorder generalised in the lymphatic tissues alone, viz., Lymphatism or "Status Lymphaticus." This will probably seem a somewhat strangely assorted group and the reasons for its formation will be given more fully in a later part of the book, but it may here be mentioned that our knowledge of the pathology of these diseases—admittedly very incomplete—does not seem to allow of any other classification without on the one hand excluding diseases which most evidently affect the blood-forming organs or on the other rendering some other group similarly ill-assorted.

The remainder of the diseases dealt with need further subdivision and it is proposed to classify the majority of them primarily according to the type of cell affected and secondarily according to whether it is formation or destruction of that cell which is in excess or diminished or disordered.

It is obvious that excessive red-cell formation may be expected to follow excessive red-cell loss and that the two processes will therefore exist side by side in many cases of anæmia. Where there is still doubt as to which is the primary lesion, difficulty will occur and again arbitrary action will have to give the direction which knowledge does not afford. Such diseases will therefore be grouped according to the most prominent clinical feature when this method seems likely to result in the classing together of similar diseases. Where this end is of less importance or impossible to attain, it may be more convenient to use some pathological or etiological factor as a basis of classification.

In whatever way we go to work we shall certainly separate the various types of so-called secondary anæmia and shall as certainly indulge in a great deal of vain repetition of signs and symptoms if we allow the separation to be absolute. We shall therefore issue a decree nisi. The "nisi" means "unless we find it more convenient to consider them all in one chapter when we will duly explain why it is done."

We can now take, in the first place, disorders affecting chiefly the red cells and can immediately reserve for subsequent consideration those in which the circulating red cells are primarily affected. This leaves us with a group of disorders including many of the most important and interesting with which we shall have to deal. A further subdivision is necessary and we accordingly take first those in which there is an excess of red-cell formation. They include only one disease which can be called idiopathic or primary, viz., Erythræmia or Splenomegalic

Polycythæmia. The second name is a little unfortunate not only because splenomegaly is not always present but because we shall subsequently see that the less we connect spleen change with the names of diseases the less shall we fall into confusion. We are hardly on the threshold of a working knowledge of that organ. The remainder of the disorders in this group may be included under the comprehensive name of Symptomatic Polycythæmia or Secondary Polycythæmia, but we make an exception (to prove the rule) in the case of a disorder of blood formation to which the name of Blood Crisis has been applied. It is a very little matter but a very interesting one. The name is applied to a condition in which there is a sudden rapid output of new red cells and it is characterised by the presence of a considerable number of nucleated red cells in the blood stream, where they ought not ordinarily to be found. It is one of those disorders which the writer prefers to call "Blood Symptoms" and is more fully dealt with on page 183. In the anæmia following hæmorrhage the essential lesion in the blood-forming organs is certainly an excessive formation of blood cells and it ought therefore to come into this group but as a matter of convenience it will be dealt with under Secondary Anæmia on page 191 and the following pages. It may be noted that this blood regeneration does not uncommonly proceed to the extent of producing an actual polycythæmia.

Those diseases in which there is a decrease of red-cell formation are also divisible into primary and secondary. The first group includes two rare diseases, viz.: Acute Aplastic Anæmia and Congenital Anæmia. Their bona fides are not beyond suspicion and they will probably be rather hardly dealt with in years to come until their claims to be clinical and pathological entities are destroyed and they take their places in the secondary group. This, at present, includes the Atrophic Anæmias (due to sepsis, bad hygiene, etc.), Splenic Anæmia of Infants and another rare disease, viz., Senile Anæmia. The latter is almost as unsatisfactory a clinical entity as are the two mentioned a moment ago. Splenic anæmia of infants is included here because the trend of opinion and of the information available is all toward a refutation of its claims to be a primary disease—

claims put forward when it was first described and suggested in the name pseudo-leukæmia then advocated.

Next for consideration are those diseases in which excess of blood destruction (as distinct from hæmorrhage externally) is the primary or at least most prominent feature. It may be mentioned that the regeneration which follows loss of blood differs in several respects from that which follows destruction of blood within the body so that this distinction is more valid than might at first appear. In the primary sub-group we have only one disease, *i.e.*, Cholæmia. This is commonly divided according to whether the disease is congenital or acquired but in order that a somewhat rare disease may be adequately discussed in one place this distinction has not been emphasised in the classification adopted as a plan for this volume. In the secondary sub-group we come at last to that most discussed of blood diseases "Pernicious" or as some, including the writer, prefer "Addisonian" Anæmia. The clinical and experimental investigations which have been conducted in reference to the etiology of this disease lead to but one conclusion, viz., that hæmolysis is the most important feature and that it is probably due to some bacterial toxin. The nature of the germ in question and its site of invasion may be doubtful but its existence is hardly in question. Very interesting is the recent production of this disease by means of bacteria of the bacillus coli group with strong hæmolytic tendencies. Associated with Addisonian anæmia we have other Hæmolytic anæmias produced by known chemical agents such as benzene. These are chiefly industrial diseases although the taking of such substances with suicidal intent does provide a few instances.

We now come to those cases in which the red-cell destruction which normally occurs is not essentially either increased or diminished but is disordered. The existence of irregularity is usually apparent from the presence of unusual products of blood destruction or from the presence of the usual products in unusual amounts or in unusual positions.

These diseases are not usually dealt with in treatises on hæmatology but although there are weighty reasons for their exception it seems almost impossible to avoid some notice of them. They are accordingly dealt with rather briefly, a task which is rendered the easier by the small amount of knowledge of them which is available. They include Hæmochromatosis or bronzed diabetes, Hæmoglobinuria and Hæmatoporphyrinuria. These are outstanding examples of disorder of blood destruction but there are a considerably larger number which are recognised in isolated cases but have not as yet been satisfactorily co-related. In fact it is almost arguable that the existence of any unusual pigment in the urine is evidence of disordered blood destruction—with certain obvious exceptions.

With the disorders of blood destruction we must also mention a blood symptom which has received various names, some descriptive, some merely inapt. It is characterised by the presence in the blood stream of actively phagocytic cells which are there engulfing the red cells and even each other. It is here described under the title Intravascular Cytophagocytosis in preference to the alternative titles such as auto-erythrophagocytosis or phagocytic anæmia.

The diseases in which the circulating red cells are primarily affected or even solely affected form a very definite group. Our knowledge of them has been very greatly added to of recent years although obvious cases of infective methæmoglobinæmia were described as far back as 1845.

The parasitic diseases it is not proposed to deal with here as to do so would necessitate doubling the capacity of the book.

Those in which the hæmoglobin is affected are four in number for all practical purposes. Firstly we have cyanosis of the usual type—a symptom of many diseases and depending on the presence of an undue proportion of "reduced" or unoxidised hæmoglobin in the blood. Secondly we have Carbon Monoxide or Coal-gas Poisoning which is the type of all the group and one of the very few disorders to which the name blood disease can be applied in its strict meaning. The two varieties of cyanosis which are distinguished by the co-existing extreme pallor and by their probable origin in alimentary disorder are sometimes grouped together under the title of enterogenous cyanosis.

This is unfortunate as they are quite distinct conditions. They are here described as Sulph-hæmoglobinæmia and Infective Methæmoglobinæmia respectively.

The diseases in which white-cell formation is primarily disordered have already been dealt with and have been seen to fall into the group of generalised affections of blood-forming organs, but as we had secondary decrease and increase of red-cell formation so also we have secondary increase and decrease of white-cell formation. These are discussed under the headings Polymorph leucocytosis, Eosinophil leucocytosis, Mixed leucocytosis, Lymphocytosis and Leucopenia.

There remain still those diseases in which the plasma seems primarily at fault. These include in the first place Chlorosis and secondly Hæmophilia and the Hæmorrhagic Disease of the New-born. The first two of these have far more in common than is, perhaps, generally recognised and it is, moreover, quite impossible to include chlorosis in any other group. The author firmly believes that this novelty in classification will be justified and certain reasons for this belief are subsequently set forth although a full discussion of the question does not accord with the purpose of this book.

Finally we must conclude with a group into which we can put disorders which must be mentioned but which seem to have little claim on our consideration as diseases of the blood, its formation or its destruction. These are Leukanæmia and Purpura. The former is a blood picture and no disease, the latter is a symptom of very many diseases and seems only entitled to consideration as such.

It will be observed that the above classification is open to all manner of objections and to the charge of inconsistency inasmuch as it includes and excludes diseases often in a very arbitrary manner. No one is more aware of this than the author, but a scientific classification is not yet possible and until it is each author's classification will naturally reflect those theories as to causation, etc., which are especially dear to him. This, it is hoped, need not detract from a study that is primarily concerned with treatment and diagnosis—problems which can only be dealt with satisfactorily in relation to any particular disease when the best working theory of its pathology is borne in mind.

The classification is finally as follows:—

GENERALISED AFFECTIONS OF BLOOD-FORMING TISSUES

PRIMARY	Leukæmias	1. Lymphæmia.
		2. Myelæmia.
		3. Chloroma.
	Hodgkin's Disease	4. Hodgkin's Disease.
	Gaucher Splenomegaly	5. Gaucher Splenomegaly.
SECONDARY		None.

LOCALISED AFFECTIONS OF BLOOD-FORMING TISSUES

PRIMARY	Of Marrow	6. Multiple Myeloma.
	Of Lymph Glands	7. Lymphoma.
	Of Spleen	8. Splenic Anæmia of Adults.
SECONDARY	Of Marrow	None.
	Of Lymph Glands	9. Lymphatism.
	Of Spleen	None.

AFFECTIONS OF RED-CELL FORMATION AND DESTRUCTION

PRIMARY	Increased formation	10. Erythræmia.
SECONDARY	Increased formation	11. Secondary Polycythæmia.
		12. Blood Crisis.
		13. Post-hæmorrhagic Anæmia.
PRIMARY	Decreased formation	14. Acute Aplastic Anæmia.
		15. Congenital Anæmia.
SECONDARY	Decreased formation	16. Atrophic Anæmias.
		17. Splenic Anæmia of Infants
		18. Senile Anæmia.
PRIMARY	Increased destruction	19. Cholæmia.
SECONDARY	Increased destruction	20. Addisonian Anæmia.
		21. Other Hæmolytic Anæmias.
PRIMARY	Disordered destruction	22. Hæmochromatosis.
SECONDARY	Disordered destruction	23. Hæmatoporphyrinuria.
		24. Hæmoglobinuria.
		25. Intravascular cyto-phagocytosis.

AFFECTIONS OF CIRCULATING RED CELLS

PRIMARY	Parasitic	26. Malaria, etc.
	Of Hæmoglobin	27. Cyanosis.
		28. Carbon monoxide poisoning
		29. Sulph-hæmoglobinæmia.
		30. Infective Methæmoglobinæmia.
SECONDARY		None.

AFFECTIONS OF WHITE-CELL FORMATION AND DESTRUCTION

PRIMARY......Increased formation.....(See Generalised Affections.)
SECONDARY...Increased formation.....31. Polymorph leucocytosis.
32. Eosinophil leucocytosis.
33. Mixed leucocytosis.
34. Lymphocytosis.
PRIMARY......Decreased formation....None.
SECONDARY...Decreased formation....35. Leucopenia.
PRIMARY......Increased destruction. ..None
SECONDARY...Disordered destruction. .None.

AFFECTIONS OF CIRCULATING WHITE CELLS....None.

AFFECTIONS OF THE PLASMA

PRIMARY............................36. Chlorosis.
37. Hæmophilia.
38. Hæmophilia neonatorum.
SECONDARY........................None.

UNCLASSIFIED AFFECTIONS............39. Leukanæmia.
40. Purpura.

CHAPTER II

THE BLOOD-FORMING ORGANS

The blood-forming organs in health are the marrow, the spleen and lymphatic tissue wherever situated. These supply to the blood the cells which are met with in the circulation. In fœtal life and possibly in the early days of extra-uterine life the liver is also a blood-forming organ. The thymus, which is atrophied in adults, is an additional blood-forming organ in the infant. It reaches its maximum size in relation to the rest of the body about the age of two years, after puberty atrophies and then is almost entirely replaced by fat.

In disease the liver and the thymus may resume or fail to lose their blood-forming functions. Thus in leukæmia of either variety and in lymphatism the thymus is often found to be present in full activity, and in some cases of congenital cholæmia the red-cell-forming function has been well marked in the liver. The latter organ invariably forms white cells in leukæmia.

In normal health the marrow alone forms red cells and leucocytes while the spleen and lymphoid tissues form only lymphocytes. There are in all probability foci of lymphoid tissue in the marrow and from these are formed a certain number of lymphocytes but they form a minority of the total and do not appreciably alter the truth of the statement that the marrow forms in particular red cells and leucocytes while the lymphocytes are formed elsewhere.

In disease any blood-forming organ may form any variety of blood cell. This fact depends on the presence in all such organs of primitive cells which are further back in the evolutionary scale than the point at which the leucocytes and lymphocytes were originally differentiated. Such cells are also found throughout mesoblastic tissues and this accounts for the further fact that in disease actual blood-forming tissue may spring up in the skin, the salivary glands, etc. It is also from these cells that the thymus is regenerated and its cell-forming activity called again into being. The leukæmic tissue met with in the liver has a similar origin.

In health certain parts of the blood-forming (or hæmopoietic) tissues have been specialised for red-cell, for leucocyte and for lymphocyte-forming functions respectively. But this specialisation is not so fixed that reversion to more primitive activities is impossible in disease. The leukæmias are the diseases in which it occurs most typically.

We can now proceed to deal with each of the blood-forming organs in more detail.

THE MARROW

This is normally found in the bones which contain cancellous tissue and is present in the centres of ossification in growing bone. It is composed of a reticulum of connective tissue containing a large number of fat cells. In parts there is among this connective tissue a specialised form which is concerned in the production of the blood cells. Where this blood-cell-forming tissue is in abundance the fatty tissue is diminished and vice versa. In adult health the ends of the long bones and the flat bones such as the ribs and fibulæ contain very little fatty marrow while the shafts of the long bones contain little else. In any disease which necessitates an extra supply of red cells or of leucocytes (but especially the former) the cell-forming marrow extends at the expense of the fatty tissue, *e.g.*, into the shafts of the long bones. Where there is a depression of cell-forming function as is the case in acute aplastic anæmia and rarely in the specific fevers, etc., the fatty marrow extends to situations not normally occupied by it.

Even a portion of the marrow which to the eye appears entirely composed of fat is seen on microscopical examination to contain minute islets of cell-forming tissue and, conversely, amongst the red or cell-forming marrow there is almost always a proportion of fat. The demarcation of the two is not as absolute as it appears to the naked eye.

The usual appearance of the marrow is that of a highly vascular dark red tissue. In septic cases and a few others it may appear of a lighter red and gelatinous transparency. This is the so-called gelatinous degeneration and is due to fatty degeneration of the cells—not to fatty infiltration. In leukæmia the marrow may be grey or even green in colour.

The cell-forming marrow is usually spoken of as red marrow. If in an adult the shaft of the femur is found to contain red marrow it is almost certain that there was during life some process productive of hyperplasia of the cell-forming tissues, *i.e.*, that for some reason there was need for an extra supply of blood cells. If the ends of the femur do not contain red marrow the reverse inference is justified, viz., that the disease present during life was of such a nature that blood formation was hindered or in abeyance. The latter rule is not, however, absolute.

The actual cells found in the marrow are red cells of the sort found in the circulation and their predecessors the nucleated red cells; the neutrophil, eosinophil and basophil leucocytes and their respective predecessors in the myelocyte series; a few lymphocytes; giant cells of various sorts and the cells of the reticular supporting tissue.

The myelocytes resemble the leucocytes in so far as their granulation is concerned but differ in the shape of the nucleus which is oval or circular and never lobed although it may be indented. There are also to be found cells which are mononuclear and have a very deeply staining protoplasm. These are precursors of the myelocytes. Mitotic figures may be found in any of these cells except the fully formed leucocytes and red cells which are ready to be passed into the blood stream.

Agents of blood destruction in the shape of phagocytes, endothelial cells, and giant cells, and the resulting pigment granules are also to be met with in the marrow.

As has already been mentioned the fatty areas contain islands of tissue similar to that found in the cell-forming areas.

THE LYMPHOID TISSUES

These include firstly the lymphatic glands. Secondly there are to be considered the thymus and the lymphoid follicles in the mouth, throat and other parts of the alimentary tract. The hæmolymph glands are a specialised variety but with this exception the above tissues and also isolated areas in the marrow and a great part of the spleen are devoted to the formation of one type of cell—the lymphocyte or hæmic lymphocyte. Their development is similar and their structure identical in so far as this function is concerned.

Anatomically there is found a collection of lymphocytes clustered tightly round a central artery with its supporting tissue. Round this again is a collection of less tightly packed cells and these are included in a loose bag of connective tissue divided up into compartments by minute trabeculæ. The meshes of this reticular tissue are occupied by lymphocytes and those towards the germ centres—*i.e.*, the central portions—show evidence of mitosis. The periphery of the gland is occupied by a lymph sinus into which the afferent vessels empty and the efferent vessels leave at the hilum.

The sinuses and trabeculæ are lined with endothelial cells.

The thymus has no germ centres but is composed of masses of lymphocytes arranged in cords amongst a reticular network similar to that of the lymph glands. These lymphocytes exhibit mitotic figures.

The hæmolymph glands differ in the fact that the sinuses contain blood—consequently they appear red in many conditions. They are placed on either side of the aorta.

In the spleen also the blood comes into direct contact with the endothelial cells lining the lymph spaces. These cells are actively phagocytic and the spleen and hæmolymph glands are both concerned in normal and pathological blood destruction.

THE SPLEEN

This organ is surrounded by a capsule which sends numerous prolongations into the substance of the organ. These divide and subdivide into very minute divisions. In the reticular tissue formed by these divisions or trabeculæ run the smaller veins and between them is a tissue known as the splenic pulp. This is composed of anastomosing columns of small, round, mononuclear cells. These are frequently aggregated into small masses to which the name of lobules is given. At intervals in the substance of the spleen are true germ centres similar to those found in the lymph glands and having a similar function, viz., the formation of lymphocytes. These centres originate in the adventitia of the arteries. There are no afferent lymph vessels to the spleen but efferent vessels arise in the lymph spaces between the columns of spleen pulp. These spaces are lined with phagocytic endothelial cells so that the spleen both forms lymphocytes and destroys red cells and leucocytes.

In disease in common with other lymphoid tissues it may manifest the ability to develop any variety of blood cell.

The function of the spleen is not so simple as the above account might lead one to suppose. If a dose of an hæmolytic poison is given to an animal it is followed by destruction of the circulating red cells and this destruction is proportionate in amount to the dose of the poison. If, however, the spleen has been first removed the blood destruction is not nearly so great. This experiment is extremely interesting as showing that the spleen has some function in relation to red-cell destruction above that of removing effete corpuscles from the blood.

The spleen also possesses rhythmic contractility and appears to increase in size during digestion. These facts point to other functions as yet imperfectly elucidated.

THE LIVER

That part of the liver which is concerned in blood formation is known as Glisson's capsule, *i.e.*, it comprises the supporting tissue around the bile ducts, portal veins and hepatic arteries, which run together in a fibrous sheath. This tissue is potentially blood-forming tissue in virtue of its content of primitive cells. In normal adult life this function is in abeyance. In disease it may be resumed.

The liver is also concerned in eliminating as bile the products of blood destruction. Whether it takes any part in the precedent hæmolysis is at present not decided.

THE BLOOD AND ITS CELLS

The blood is composed of a clear yellowish fluid in which float a great number of various cells—the red cells or erythrocytes predominating.

The fluid is called the plasma; the cells are divided into groups, the red cells and the white cells. The nature and functions of these will presently be discussed.

The plasma is the great carrying agent of the body and all products of metabolism pass through it on their way to absorption or excretion. Of recent years a large number of bodies have been described in it and have each received several names. Whether these bodies are often the same under different names and whether they are formed in the plasma or in the cells of the body from which they are shed into the plasma is a matter on which conflicting views are held. The study of the plasma is thus very largely hindered by the lack of any knowledge of the actual constitution of bodies whose presence is only determined by their activities. When this knowledge is available there will be opened up a chapter in biology as greatly in advance of our present humeral pathology as is our hæmocytology in advance of that which obtained before the discovery of aniline dyes. At present we can study the changes in the blood cells as we meet with them in disease but are little able to explain the purpose or genesis of the various alterations encountered. Then we may be able to understand on what subtle bio-chemical processes these alterations depend and assert with some confidence the part which the blood cells play in the preparation of our defensive forces against bacteria and in the maintainance of life. That the plasma and the cells work together can hardly be doubted, but at present the cells are much more easy of investigation.

We have already mentioned that many of the bodies present in the plasma are very probably formed by the cells of the organism and then shed into the blood; in the same way it is well to bear in mind that the cells of the blood are not formed in the circulation but are shed into it from the blood-forming organs, nor do the proportions in the blood necessarily reflect those in the organs in question.

The Red Cells.—The red corpuscles are minute concave discs and they are not red but yellow. In a very thin film they are not such powerful absorbents of light as in a thick layer. This is natural enough. In the thin film they allow red light to pass through but they also allow the passage of yellow light and this "drowns" the red so that the eye sees a thin film or a single corpuscle as a yellow object. A thick layer does not allow the passage of yellow light and in consequence the red is able to hold its own (in the absence of competitors) and the eye sees red. The red colour is due to the presence in the corpuscles of a pigment called hæmoglobin and this is present in the walls of the cells and not evenly diffused through their substance. The wall is made of a denser substance than the contents and is extremely elastic: with it is incorporated the hæmoglobin. There is no nucleus in the ordinary circulating red cell which is derived from its predecessor the nucleated red cell by extrusion or solution of the nucleus. The nucleated red cells in turn are derived from cells which lack hæmoglobin. The red cells are in number about 5,000,000 per cubic millimetre, but the possible variations in health are rather large. On the one hand 4,500,000 and on the other 7,000,000 may be met with in apparently normal and healthy persons. 5,000,000 is usually given as the average but is probably too low by about half a million. They are formed in the marrow and destroyed in the spleen, the pigments resulting from their destruction being excreted by the liver in the bile.

Owing in part to their shape and in part to the chemical nature of their envelopes they tend to adhere to each other and form long rolls like piles of coins. This is called rouleaux formation. It is occasionally modified in disease but is very seldom absent even in the severest anæmias.

The red cells are the great oxygen carriers of the body. They carry oxygen by virtue of their hæmoglobin which unites with it in a loose chemical combination possibly analogous to the combination of a salt with its water of crystallisation.

The resulting compound is called oxyhæmoglobin and this deprived of its oxygen is called hæmoglobin or "reduced" hæmoglobin. The name "reduced" is unfortunate as it implies something different from hæmoglobin alone, whereas the two are identical.

Hæmoglobin is of a darker colour than oxyhæmoglobin and hence its presence in any great amount gives rise to an alteration in the colour of the blood. This is seen in the bluish colour of venous blood and in the characteristic colour of cyanosis.

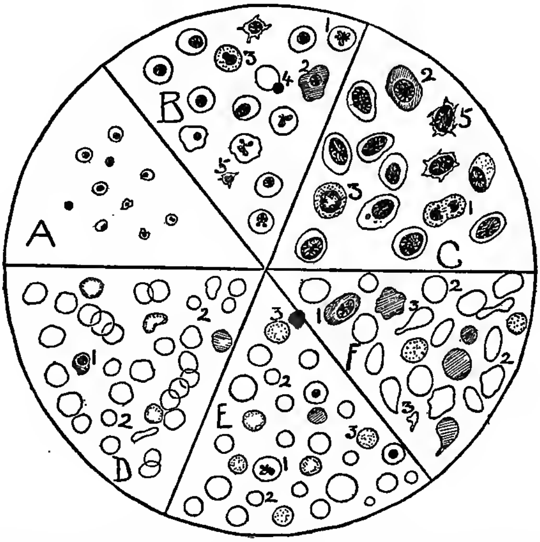


Fig. 1.—Diagrammatic representation of the red blood corpuscles. *A*, Microblasts; *B*, Normoblasts showing (1) mitosis, (2) polychromasia, (3) stippling, (4) extrusion of the nucleus, (5) almost entire absence of protoplasm; *C*, Megoblasts showing (1) mitosis, (2) polychromasia, (3) stippling, (5) almost entire absence of protoplasm; *D*, the blood in chlorosis and secondary anæmias, *i.e.*, of the "chlorotic" type, (1) a normoblast, (2) microcytes; *E*, the blood in congenital cholæmia or acholuric jaundice; (1) a normoblast undergoing division, (2) microcytes, (3) stippling; *F*, the blood in "pernicious anæmia" (Addisonian anæmia), (1) a megaloblast, (2) a megalocyte, (3) poikilocytes.

The Nucleated Red Cells.—These are the precursors of the red cells of the circulation and differ from them chiefly in the presence of a nucleus. They are divided into three classes according to their size (Fig. 1). This division is very largely artificial. The larger cells are named megaloblasts and have a nucleus which takes up the greater part of the cell and sometimes stains very diffusely. The second class, of the same size as the normal red cells, are called normoblasts and in these the nucleus stains very deeply, while the remainder, composed of very small cells, are called microblasts. The latter have very variable nuclei and may be portions of larger cells which have become separated. It will be found in practice that the size of the cell, although the ostensible basis of classification, is an entirely untrustworthy guide and much more reliance is to be placed on the nature of the nucleus. Even then various intermediate nuclei will be met with and render the artificial nature of the classification clear. Fortunately there is little practical advantage to be drawn from a consideration of the shapes or sizes of the nucleated red cells which may be present in a blood film.

Each of these nucleated red cells is supposed to give rise to a non-nucleated cell of the same size and these are accordingly named megalocytes, normocytes or erythrocytes (the normal red cell) and microcytes.

The term erythroblasts includes all varieties of nucleated red cells.

The White Cells or Leucocytes.—The white cells are all nucleated and are normally present in the blood to the extent of 6000 to 8000 per cubic millimetre only. Very rarely they reach 12,000 in apparently normal healthy adults but this figure is not uncommon in children below 14 years of age.

They are conveniently divided into two classes according as they are normal or abnormal inhabitants of the blood stream (Fig. 2).

The former are named as follows and exist in the proportions indicated.

It will be observed that many of them rejoice in more than one name.

The *polymorph* or *polymorphonuclear neutrophil leucocyte*, or finely granular or neutrophil leucocyte or simply "leucocyte" is the commonest white cell in the blood. This cell is present in the proportion of 50–75 per cent. of all the white cells, reaching a total number per c.m.m. of 5–7000 in health, It is so named because it contains a polymorphic nucleus. The nucleus often appears to be divided into several distinct parts, but these are as a matter of fact joined by a thread of nuclear substance which is very often obvious. The nucleus stains very deeply, especially in old cells, and the cytoplasm contains minute granules which stain faintly with eosin. These are the so-called neutrophil granules. They received this name under a misapprehension and have now been shewn to be oxyphil, *i.e.*, to possess an affinity for acid dyes.

The *eosinophil leucocyte* or coarsely granular cell is similar to the polymorph except that it is a little larger, has seldom more than two lobes to the nucleus and possesses much larger granules. These granules stain with an acid dye, *i.e.*, red with the stains usually employed.

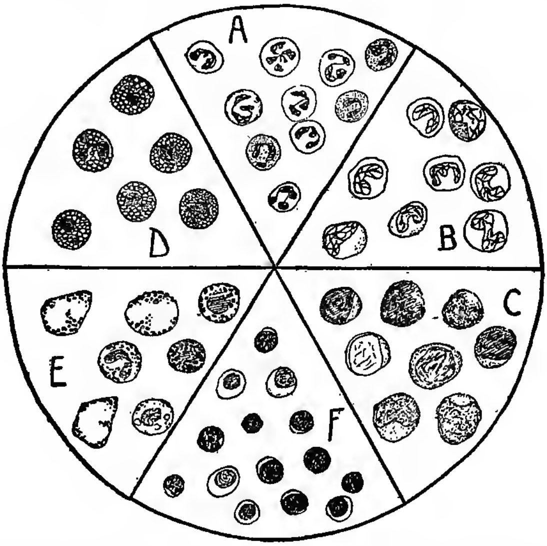


FIG. 2.—The white cells or leucocytes of normal blood showing the variations met with and the effect of different stains and of different intensities, etc., of the same stain. *A*, Polymorphonuclear leucocytes or "leucocytes"; *B*, transitional leucocytes; *C*, large mononuclears, large hyaline cells or large monomorphs; *D*, eosinophil leucocytes; *E*, basophil leucocytes, mast cells; *F*, lymphocytes, small mononuclears.

The eosinophil is present to the extent of 150–250 cells per c.m.m. and forms from 0.5 per cent. to 2 per cent. of the white cells. It is slightly more numerous in childhood and is physiologically increased during menstruation.

The *mast cell* or *basophil leucocyte* is easily distinguished from the last two by its granules which are irregular in size and stain of a purplish colour. This is due to the fact that they take up both blue and red stain in a mixture such as Wright's stain; from this property they are called metachromatic. They form a very small percentage of the white cells, as a rule less than 1 per cent.; it is often the case that in the course of a differential count no single mast cell is met with.

The *transitional leucocyte* is similar to the polymorph in many respects and is a younger form of that cell. The nucleus, although not partite, is lobed and convoluted. It is of a more open texture and stains less deeply than that of the polymorph. The cytoplasm stains bluish and is devoid of granules in some cells, in others it contains minute acidophil granules. It is probable that these granules are always present but as a matter of practice they are not always easily demonstrated. This cell forms a very varying percentage of the white cells in disease but in health usually between 2 per cent. and 5 per cent. It is increased in most cases of leucocytosis. There is a similar early form of the eosinophil distinguished by the same differences in the nucleus but this is not very often met with in health.

The *small mononuclear* or *lymphocyte* or small lymphocyte is, next to the polymorph, the most commonly met with of the blood cells. It forms from 15–30 per cent. or even more of the total white cells and the absolute number varies from 1500 to 3000. Both these numbers and some of those given above allow a larger margin in health than is usually admitted but there can be no doubt that these large variations do exist in people who appear healthy and in such circumstances that it is impossible to attribute them to any physiological process such as digestion, sleep, etc.

The lymphocyte is a small cell and the nucleus stains more deeply than that of any other mononuclear cell with the exception of the nucleated red cell. The cytoplasm stains bluish and less deeply than the nucleus. If the smear which is being studied has been well stained there may be a few largish granules of a reddish colour in the cytoplasm but these are not always seen. It should be remembered that towards the extreme edge of the film where the stain has not perhaps been so strong or where some unknown factor has been in operation the cytoplasm may stain more deeply than the nucleus. This, of course, implies an error in technique but is none the less worth mentioning as errors in technique are not very rare.

Moreover the size of the lymphocyte and the relative amounts of nucleus and cytoplasm may vary as the result of the pressure exercised in making the film and also according to the age of the cell, the younger cells tending to be larger than the others.

This larger cell has been called the *large lymphocyte* but there is no apparent advantage in insisting on this difference as the cells are essentially the same and the introduction of the second term is apt to lead to confusion with the large mononuclear.

The large mononuclear is a cell of which the parentage is in doubt as are also its use and eventual destination. There are also differences of opinion as to what exactly constitutes a large mononuclear or hyaline cell. For practical purposes and to avoid an excursion into purely theoretical realms we can say, that in health any cell which is not a lymphocyte and has not a lobed nucleus is a large mononuclear. There is little practical importance attached to their more accurate definition. They are present to the extent of 1–3 per cent. of all white cells.

The cells present in the blood in disease which are absent in health are as follows:

The Myelocytes.—These are cells resembling the leucocytes as regards their granulation but differing in the shape of the nucleus and in their size. The nuclei are oval, circular or reniform and the whole cell is much larger than the leucocyte. There are three varieties, named according to the granulation, respectively, the neutrophil, eosinophil and basophil or mast cell myelocyte. These are the immediate progenitors of the corresponding leucocytes. They are present in myelæmia and the neutrophil variety is not uncommonly met with in small numbers in any severe anæmia or prolonged or acute leucocytosis.

The Pre-myelocytes.—Under this heading may be included a great variety of cells which differ so much that they have consistently defied classification. The type cell is one with an oval nucleus which occupies the greater part of the cell and is surrounded by a rim of protoplasm which stains a very deep blue—a deeper blue than does the nucleus. This cell has two or more well marked nucleoli. Myelocytes have no nucleoli. This cell is met with occasionally in various anæmias and in leucocytosis and practically always in the acute forms of Leukæmia (both varieties) and in the chronic cases of myelæmia. It is by no means impossible that this cell is the primitive cell already mentioned with some frequency, it is certainly but little removed from a rather controversial cell—the plasma cell—with which we have little to do from a practical standpoint although its genesis is extremely interesting.

Rieder's Lymphocytes.—These cells resemble the ordinary lymphocyte in all but the shape of the nucleus. This is lobed or twisted in a way that recalls the polymorphonuclear cell. This distortion is said by some to be a degenerative change. It may be, but that is of no importance as a rule; the chief point about this cell is that it may form the vast majority of the white cells in lymphæmia of the chronic variety. It is seldom met with in any other condition.

In acute lymphatic leukæmia the cells, although resembling the ordinary lymphocyte, have ragged protoplasm, show mitotic figures and usually vary a great deal in size—more than is the case in normal blood.

It is not infrequently a matter of difficulty to determine to exactly what group any particular cell belongs and this is especially the case in leukæmia. In this disease it is usually enough to know that leukæmia does exist and in others these cells are not met with in such numbers as to invalidate the deduction which may be drawn from any particular examination of the blood.

The Blood Platelets.—These bodies have given rise to considerable controversy. Some authorities deny that they are to be found in the living blood and assert that they are artifacts produced in the preparation of films or at the moment that the blood leaves the circulation.

Whether artifacts or not they are certainly facts and as such must have some significance. At present we do not know what this significance may be but they have been noted to be absent in many cases of the so-called hæmorrhagic diatheses, *i.e.*, in purpura, in acute aplastic anæmia, etc.

They are of varying size according to the method employed in preparing them for observation. In a fresh wet film they are about one-fourth the diameter of a red cell or even less. They contain a central chromatin mass which may be called a nucleus and when the blood clots they become vacuolated. This may merely mean that they die or may, as is most probable, portend some close connection with the clotting.

Their origin is obscure and they are variously reported as arising in the giant cells of the marrow, from the disintegration of leucocytes or red cells and from precipitation from the plasma in which they are then assumed to have been previously in solution.

They number about 200,000 per cubic millimetre.

Hæmoconia.—This name is given to various minute granules seen in the blood under a high magnification. Their origin and significance are alike unknown. The term blood dust is also applied to them.

CHAPTER III

METHOD OF MAKING A BLOOD EXAMINATION.

The following are necessary for a full blood examination:

A microscope with No. 2 eyepiece and 2/3rd, 1/6th and 1/12th (oil immersion) lenses. A movable stage is a decided advantage but is not absolutely essential for rough work.

A small bottle of cedar oil.

Some squares of butter muslin to use as cleaners.

A counting chamber and pipettes—these are contained in the Thoma-Leitz hæmocytometer.

Haldane's hæmoglobinometer (or some other form).

A packet of triangular pointed surgical needles or a sharp lancet.

A bottle of Hayem's solution of which the composition is as follows:

Perchloride of Mercury	0.5 gm.	or 8 grains.
Sodium Sulphate	5 gms.	or 77 grains.
Sodium Chloride	1 gm.	or 16 grains.
Distilled Water	200 gms.	or 7 fluid oz.

This is the diluting fluid for the red corpuscles.

A bottle of 0.5 per cent. acetic acid to which has been added a trace of methylene blue. This is the diluting fluid for the white cells.

A bottle of Wright's stain, Giemsa's, or Leishmann's stain.

A bottle of distilled water.

A bottle of alcohol.

A bottle of ether.

A case for holding slides.

Slides and cover-slips.

The method of using the foregoing is as follows:

Obtaining the Blood.—A prick is made in the patient's ear in the most dependent part of the lobe. The first drop of blood which appears is wiped away. Then blood is sucked up into the hæmoglobinometer pipette to the 20 cm. mark and immediately ejected into the graduated tube supplied with the hæmoglobinometer. There should be a little distilled water in the bottom of this so that the blood lakes at once and does not clot. The mixed blood and water should be drawn a few times up and down the pipette and the latter then put aside until it is convenient to clean it.

Then blood is drawn up in the red cell pipette, that which is marked 101 at the top of the bulb. It is drawn up to the 0.5 mark and then Hayem's solution to the top of the bulb. The pipette is rolled horizontally on the palm of the hand to ensure proper mixing—which is very important—and then put aside.

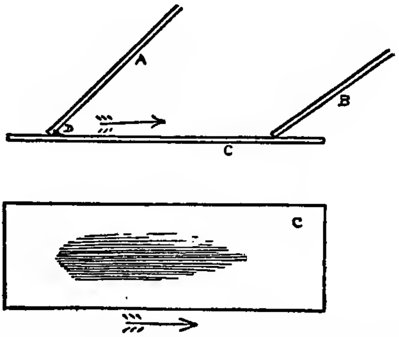


FIG. 3.—Method of making a blood film and the film when made. The blood smear should in no case reach either end of the slide as this means that some of the larger cells (*e.g.*, polymorphs) will be carried right off the slide and the differential count will be inaccurate in consequence. The smaller lymphocytes which remain behind will appear to be present in unduly large proportion.

Blood is next drawn up in the remaining or white cell pipette to the 0.5 mark and the blue diluting fluid to the top of the bulb. Mixing is carried out as before and the pipette put aside.

It may be mentioned that, if it is necessary to carry the pipettes after filling from one house to another, it is well to remove the bone mouthpiece from the rubber tubing attached to the pipette and then to turn the free end of the tubing over the free end of the pipette. If this is done carefully and the pipettes are kept in a horizontal position they may be safely transported.

To make the blood smears or films a very small drop of blood is necessary and a large drop is a disadvantage. It is best secured by just touching the top of a drop of blood as it exudes from the puncture with one end of a clean slide. It is then spread along the slide with the edge of another as shewn in the illustration (Fig. 3). The smear should not extend the whole length of the slide as this introduces inaccuracies in the differential count. Three smears should be made in this way and when dry will keep without further treatment for some weeks.

The material thus obtained suffices for an ordinary blood examination. Before discussing the method of obtaining the blood for other purposes it will be convenient to detail the further steps in the ordinary "blood count."

Blood Count.—The tube containing the hæmoglobin solution has now to be "gassed" which is the same procedure that it is subjected to in the living subject in coal-gas poisoning (*q.v.* page 283). The Haldane apparatus includes a piece of bent metal tubing which can be attached to any gas jet. The other end is inserted into the mouth of the graduated tube until the air is driven out when shaking turns the blood a bright red colour. This is then diluted with distilled water until it corresponds in depth of tint to that in the standard when the percentage is read off on the graduated tube. This is the percentage of hæmoglobin as compared with the normal of 100 per cent. The "gassing" is rendered necessary owing to the impossibility of obtaining a stable standard for comparison with simple diluted blood. Such standards do exist but are not satisfactory.

If the patient is obviously very anæmic it will be found a good plan to use twice the amount of blood that is usual for this estimation. The author uses a pipette graduated to 10, 20, 30 and 40 c.m., but otherwise resembling Haldane's. With this larger or smaller amounts can be taken in anæmia and polycythæmia respectively.

For counting the cells there is provided a glass slide in the centre of which is a circular well which, in turn, contains a circular glass table of which the surface is lower than that of the rest of the slide. Onto this table a small drop of the diluted blood is placed after the pipette has again been rolled on the hand to ensure mixing. The first few drops of blood from the pipette must always be rejected as they contain chiefly mixing solution and very little blood. The drop of blood is covered with one of the glass slips provided and it will be seen that the lower level of the circular table allows it to spread out in a thin film of uniform thickness.

Part of this table is ruled into 400 small squares which are divided into groups of 16 by lines which intersect every fifth row of squares. This ruling is apparent when the drop of blood is looked at under the microscope; if the 2/3rd power is employed the whole of the 400 squares can be seen but if the 1/6th only one group of 16 small squares is contained in the field.

For *counting the red cells* the 1/6th power is necessary.

When the diluted blood is focussed with this the cells are found to have settled down over the squares so that they are easily counted. It is necessary to count the number of cells in each of five successive groups of 16 small squares. Three such groups should be counted in one drop of blood and two in another. If the numbers so obtained are fairly near to each other the whole five are added together and four naughts (0000) added on to the end. This gives the number of red cells per c.m.m.

Thus if the five successive groups of 16 squares contained respectively 92, 105, 88, 96 and 101 cells, the total is 482 and therefore the number of red cells per cubic millimetre is 4,820,000. If the numbers do not agree with each other two further drops should be counted and so on until a fair average is obtained. By counting only one drop one is spared the worry of discordant figures and also a good deal of time but the results have no scientific value.

The *white cells are counted* slightly differently. In the pipette to which the blue diluting fluid was added the red cells are invisible, having been dissolved by the acetic acid. The white cells are on the other hand rendered more obvious by the blue stain. They are best counted under the 1/6th power but more easily under the 2/3rd if the light be carefully arranged. In either case it is necessary to count the whole of the 400 squares in each of two drops of diluted blood. The resulting two numbers if they are more or less similar are added together and two noughts added to them. This gives the number of white cells per c.m.m. Thus if the number in the first drop is 43 and in the second 48 the total is 91 and the number of white cells per c.m.m. is therefore 9100.

As was the case with the red cells it may be necessary to count the cells in a further two drops of diluted blood, afterward taking the average.

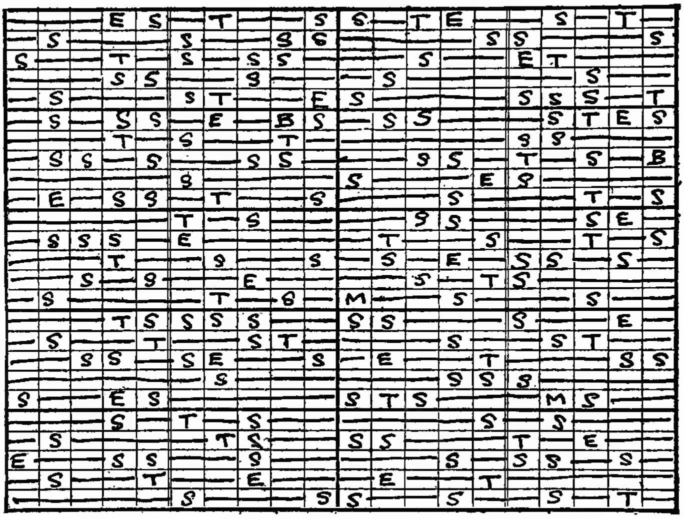


FIG. 4.—Illustrating method of making differential count of white cells on squared paper. For every polymorph seen a square is crossed through. Other cells are represented by letters, E, S, T, etc. The amount of writing necessary can be much shortened. See Fig. 5.

We have now noted the methods of carrying out the hæmoglobin estimation and that of estimating the number of red and white cells per c.m.m. The differential count has next to be considered. This is the estimation of the relative proportions of the different white cells by examination of a stained film.

One of the films spread when the blood was taken is flooded until all the blood smear is covered with Wright's stain. The slide is covered with a watch glass or any convenient object to prevent evaporation and left for two minutes. Distilled water is then added until there appears a greenish scum on the surface of the stain. This means that about as much distilled water must be added as there was stain used. This is left a further three minutes and the slide is then rapidly washed under the tap and stood on end until dry. It is then ready for examination and should not be covered with Canada balsam or a glass cover-slip as this is not only unnecessary but prevents restaining and assists fading of the stain.

When the slide is dry a drop of cedar wood oil is placed directly on to it and it is examined with the oil immersion (1/12 inch) lens. Pure liquid paraffin may replace the oil.

The object of the **differential count** is to determine the relative numbers of the various kinds of cells met with. Passing along from one end of the smear to the other and back at a lower level (it is in this that a mechanical stage is so convenient) the numbers of each different cell are noted on paper and from this the relative numbers calculated. The author is accustomed to use paper ruled into squares for this purpose. An accurate result cannot be obtained unless at least five hundred cells are counted, and by the use of paper ruled into five hundred squares and subdivided as shown in the illustration (Fig. 4) it is at once apparent when five hundred have been counted and is easy to reckon the proportions of each. The method adopted is to assign a letter to each cell such as E for eosinophil, B for basophil or mast cell and M for large mononuclear. As the cells are met with the appropriate letter is noted in a square and so on until all 500 squares are full. As polymorphs are so frequently met with it is better not to denote them by a letter but to merely cross through a square.

After a time, especially if much blood counting is done, it becomes easy to carry the numbers of polymorphs and lymphocytes in the head. The other cells are put down as they are met with. Thus at a certain stage one will perhaps have met with 42 polymorphs, 12 lymphocytes, 2 eosinophils, 3 transitionals, etc. All but the polymorphs and lymphocytes will have been put down, *i.e.*, recorded by the filling in of a square, the latter will be kept in mind by repeating the numbers 42, 12. If then two more lymphocytes and one polymorph are met with one adds these and repeats 43, 14, and so on. The author has as a rule no difficulty in keeping these numbers in his head up to 100 polymorphs. It is then better to put them down and it will now be apparent that the whole 100 can be recorded by crossing through a group of 100 squares which wastes much less time than the method of filling each square separately. The same, of course, is true of the lymphocytes.

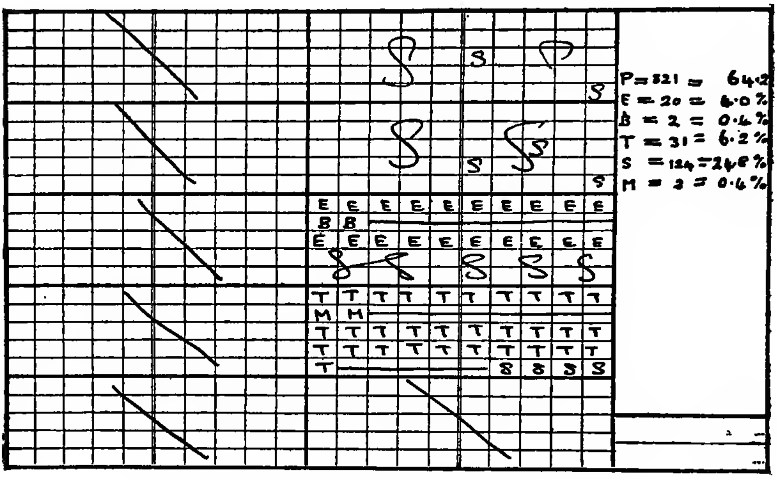


Fig. 5.—Illustrating shortened method of making differential white cell count on squared paper. The numbers of polymorphs and lymphocytes are carried in the head until 50 of the former have been met with. These are then recorded by crossing through a block of 50 squares. The lymphocytes are similarly recorded by writing S in the appropriate square—in this case the 26th, the 50th, etc. Other cells are put down as they occur, one line of 10 at a time being reserved for each.

Appended is an illustration (Fig. 5) of the squared paper used by the author, the count being a genuine one taken from a case of ankylostomiasis. It will be seen that by starting the record of the polymorphs at the top of the left hand column and the lymphocytes at the top of the right while the other cells are put in one of the groups of cells lower down on the right much time is saved in calculating the results and in recording the count. For cells other than polymorphs and lymphocytes it is sufficient to allow one line at a time and when this is filled up to start another line of ten squares.

From the percentages thus obtained the actual numbers of each cell per c.m.m. can be reckoned. It may be mentioned that the percentage of any cell is the actual number counted multiplied by two and divided by ten. This is simpler than dividing by five as the ten merely consists in putting a decimal point. The extent of the necessary calculations is shewn in the illustrations.[1]

We have now dealt with the usual "Blood Count" and it remains to mention certain other procedures which are of use.

It is often useful to **examine a fresh blood** film, *i.e.*, a specimen of undried blood. This is done by placing a small drop (it must be small) of blood on a slide and immediately covering it with a glass cover-slip. This is then ringed round with vaseline to prevent evaporation and drying. The examination of such a film will often enable a diagnosis of leukæmia to be verified without staining a film although a little experience is necessary to do so. In such films may also be seen the minute parasites of malaria and the larger ones of filaria, either of which may show active movement for some time. The spirochete of relapsing fever and various other organisms can be similarly identified.

Coagulation Time.—The time taken by the blood to coagulate is another estimation that is sometimes of use (*e.g.*, in hæmophilia and obstructive jaundice) and may be roughly estimated in the following manner. A drop of blood is placed on the slide and at half-minute intervals—from the time that the drop first appeared on the ear—is touched with a fine needle. After a time the needle will pick up a very thin thread of fibrin and then coagulation is taken to be complete. The time is then reckoned from the beginning of the experiment and this is the coagulation time. This method makes no pretense to strict scientific accuracy but is convenient when it is necessary to observe whether the coagulation time is delayed. If the time taken exceeds three minutes, coagulation is delayed.

---

[1] These illustrations are part of the author's hæmatological charts which may be obtained from Messrs. Bailliere, Tindall and Cox, London.

Thus in a case of obstructive jaundice the author found a coagulation time of nine minutes by this method. The patient was operated on the same day and died on the next from oozing into the peritoneal cavity. In cases in which the coagulation is hastened this method is not sufficiently accurate and some other must be used. Other methods are not described here because it seldom if ever occurs that in general practice it is desirable to know whether the coagulation time is or is not hastened. They are moreover rather complicated.

The amount of **fibrin in the blood** is increased, especially in lobar pneumonia and acute rheumatism. With practice such an increase can be detected in the living films previously described—in which after a while the fibrin network is quite distinct and forms a very striking picture.

The **spectrum given by the** blood is of importance in some diseases. Given a spectroscope, the blood used in estimating the hæmoglobin is usually sufficient for examining the spectrum. Otherwise a few drops must be taken into water in some glass vessel.

CHAPTER IV

GENERALISED AFFECTIONS OF BLOOD-FORMING TISSUES

In the group of diseases now to be discussed the common and distinctive feature is involvement of all the blood-forming organs by a growth or overgrowth that is similar in each organ.

In the first sub-group, the leukæmias, not only the adult blood-forming organs, marrow, spleen and lymph glands are affected but in other situations tumors may appear which are composed of tissue identical with that in the marrow, etc. These tissues are the embryonic and infantile blood-forming organs, the liver and thymus, and, secondly, connective tissue wherever met with. This extraordinarily wide distribution of lesions in some cases is the more readily explained when we remember that all mesoblastic tissue is potentially blood-forming—*i.e.*, blood-cell-forming—just as it is potentially sarcomatous or fibromatous.

In the second sub-group which contains only one disease, Hodgkin's disease, distribution of lesions is not so wide for besides the blood-forming organs the skin alone is at all commonly affected. The connective tissue in other parts of the body does not as a rule give rise to growths, although they have been recorded in the dura mater.

In the third sub-group which also contains only one disease the distribution is even more restricted for there are no lesions except those of the blood-forming organs. However, we must at least accept the possibility that in the Gaucher type of splenomegaly there will be reported some day lesions of the skin or periosteum.

The cells which compose the characteristic lesions of these diseases may be found in the blood stream, as one would expect. This however is only the case in the first sub-group and not even in all cases then. There are some cases of leukæmia in which the blood is free from abnormal cells. This is also the case in animals which suffer from leukæmia. In chickens it has been possible to transmit the disease from one animal to another and when several animals have been infected from one source it is found that some develop the lesions in the blood-forming organs but do not shed the abnormal cells into the blood stream, while others show the same lesions in the marrow, etc., but in addition a large increase in the circulating white cells.

These diseases show no tendency to pass into each other nor is this to be expected. Nevertheless they have an evolution of their own and this consists in the replacement of the more fully specialised cells which are common in the early stages by cells of a more primitive nature. Thus in myelæmia the fully formed eosinophil and other myelocytes may slowly disappear from the blood and from the marrow while their place is taken by pre-myelocytes or mother cells of less specialised nature. There is, if one may use such an expression, a progress backwards. Much less commonly the progress goes the other way and, coincidently as a rule with improved health, primitive cells are gradually replaced by those which are more fully formed.

One can perhaps make this point a little clearer by borrowing an analogy from another example of evolution. Thus the gorilla and the chimpanzee are as nearly related as are myelæmia and lymphæmia and each is but one stage in an evolutionary scale which descends from a more primitive form common to both and continues to a form which future years may show to be much in advance as far as specialisation is concerned of the present. Thus if we go far enough back we find a form which may be said to be the mother form of both gorilla and chimpanzee as we may find a mother cell which is potentially the parent of either lymphocytes or myelocytes. But we cannot trace any transitional stages between lymphocytes and myelocytes or between gorilla and chimpanzee without tracing back to a primitive source from which the transition and the types have all alike been derived.

We may even take the analogy further. If the parent form of gorilla and chimpanzee be traced back it, in turn, is seen to be merely one type descended from an even more remote primitive stock. Another derivative of the same stock has given rise to man. So also the common ancestor of lymphocyte and myelocyte is but a variation from the common stock which produced not only the ancestor in question but also the other derivatives of embryonic mesoblastic tissue, the plasma cell, the fibroblast, etc.

As however in the case of the anthropoids so also in the case of the body cells. We know that they have been thus derived but we do not know the order in which each type has been evolved nor can we always place with certainty in the evolutionary scheme any individual we may meet with.

The transition forms have been less studied in the case of Hodgkin's disease and the Gaucher type of splenomegaly than in the leukæmias but enough is known to prove the general truth on which their appearance in one class rests. In Hodgkin's disease well recognised differences are met with in the lymph glands in acute and chronic cases respectively and even in different chronic cases. In Gaucher splenomegaly all transitions have been noted in the marrow between the ordinary myelocyte and the large almost translucent cell characteristic of the disease.

We can now pass to the systematic description of the diseases in this group.

LYMPHÆMIA

Synonyms.—Lymphatic leukæmia or leucocythæmia, lymphocythæmia, pseudo-leukæmia, chloro-leukæmia, etc.

Definition.—An apparently purposeless overgrowth of lymphocyte-forming tissues reflected in the blood stream by a varying increase of lymphocytes or their forerunners.

Nature.—At present we are obliged to look upon this disease, as also on its close ally myelæmia, in the light of very insufficient knowledge. There are some reasons for supposing that it may be infective in nature and with these the writer finds no fault except that they are merely conjectural. On the other hand the theory that we are dealing with a malignant growth is not very satisfying. Even when all facts are taken into consideration we cannot be at all dogmatic as to the nature of this disease. The writer inclines to the view that it will eventually be found to be of infective and probably of intestinal origin.

General Pathology.—The pathology of this disorder is best understood if we start from a supposition which is at present unfounded but which has as much to recommend it as any other which seeks to provide an adequate "cause" for the disease. We shall suppose then that the primary lesion is a destruction of circulating white cells through the agency of some microbic toxin.

It is well known that the most powerful and efficient stimulants of blood regeneration are the products of blood destruction. This is well shewn in the case of Addisonian anæmia and in the results of injections of very small quantities of blood in cases of anæmia (see page 344). We need not then be surprised if after this destruction we find excessive formation. We do as a matter of fact find both excessive formation of white cells and the presence of the products of excessive destruction in the urine. The next step in the pathology will be the reversion of the cell-forming organs to a more primitive type as a result of the continued strain on them. This also we find in lymphæmia as we do in Addisonian anæmia. Here, however, the analogy ends for the reversion in the case of lymphæmia may proceed to the extent of resurrecting tissues whose cell-forming days were over. This has already been dealt with (page 49). Next, the hypertrophy of the lymphocyte-forming tissues will exercise effects on the surrounding structures and with these effects the pathology and the course of the disease in any individual case commonly terminate. Amongst them are a severe anæmia due to crowding out of the marrow with lymphocyte-forming tissue and disturbances of respiration, etc., due to pressure by the enlarged glands on vital structures. Less commonly the actual cause of death is dependent on the anæmia which produces fatty changes in the vessels and permits hæmorrhage. Another and a commoner termination is due to the soft and ill-resisting nature of the lymphoid infiltrations, especially that of the gums, which allows septic infection and death from septicæmia.

The course of the disease as detailed above (the morbid anatomy is dealt with elsewhere) is subject to variations in many respects. The only one of present importance is that which is occasioned by a remission—presumably a ceasing activity of the organism which is imagined to underly the manifestations of disease. The organism is perhaps as it were temporarily intoxicated with the exuberance of its own toxicity. Herein there is a further parallel with Addisonian anæmia.

Etiology.—Of this there is nothing further to be said for factors which predispose to the disease or determine its onset are not recognised. It is true that in certain cases the disease has apparently followed exposure or other debilitating factors, but these are not constant. The writer has seen lymphæmia follow an attack of whooping cough—which may of itself give rise to a very considerable lymphocytosis—but there is little enough evidence to suggest that this was more than a coincidence.

Age.—The disease shows a distinct partiality for children as far as the acute form is concerned but on the other hand the chronic type is almost if not quite exclusively a disease of adults. Cases have been recorded in the aged, for example at 60 and 70, but are rare, while at the other end of the scale are reported congenital cases. The writer does not however know of any authentic case which was congenital and the point must be considered to some extent undecided. The acute form also occurs in the aged.

Sex.—There is a distinct predilection for the male sex. This is so marked that one may say that roughly twice as many males as females are affected. Moreover most of the cases recorded in persons over seventy have been in males and of these there are several. In females the onset of the disease is rare after fifty and almost unknown after seventy. The male, therefore, not only suffers more frequently but does not escape the disease even in old age.

Onset.—This varies considerably but is as a rule gradual, the first symptoms being ill-defined and of a general nature.

In some cases the apparent onset is more dramatic although careful enquiry will usually reveal a longer history than that first given. Thus a profuse hæmorrhage may appear to be the starting point of the disease and may take place from the gums, nose, stomach, etc.

In other cases—and this is quite common in the acute cases—the first sign of note may be acute stomatitis with necrosis and gangrene of the gums or the latter may be so swollen that they cover the teeth and protrude between the lips. Chiefly in those cases which have eventually been found to be associated with green pigmentation exophthalmos has been remarked as the first symptom of the disease; in a few instances skin nodules have been seen and even carefully watched for years before any anæmia occurred.

The latter obviously include some of the chronic cases but in the majority of these swelling of the lymph-glands is the first sign and often for some time the only sign.

From these facts alone it is obvious that the diagnosis may at first present considerable difficulty.

General Symptomatology.—The symptoms are dealt with more in detail subsequently but certain features may be noted here. All the symptoms are ultimately referable to either (1) the mechanical effects of hyperplasia of lymphoid tissue, (2) anæmia or (3) toxæmia.

In the first group are a vast multitude of very dissimilar manifestations. These include all those which can follow tumour formation in any part of the body except the nervous system. Even the latter may be affected by pressure of tumours on the dura mater or even by pressure from within following tumour formation about the vessels of the choroid plexus. One case which showed the latter complication is certainly on record and very many which showed the former.

The excretion of the cells formed by the hypertrophied glands may produce a copious deposit of urates in the urine or may even cause albumosuria of the Bence-Jones type. The latter, of course, is more constantly associated with multiple myeloma (see page 134).

On the whole the results of lymphoid hyperplasia are more commonly an annoyance than a real danger to life, *i.e.*, as far as purely mechanical effects are concerned.

The results of anæmia are more familiar and when seen arouse less surprise. The most important result is certainly fatty degeneration of the heart and vessels. To this is to be attributed the dilatation of the former organ and the peculiar fragility of the vessels which allows of hæmorrhages externally and the various forms of purpura.

Malnutrition is of course a usual result of the anæmia but as a matter of fact is seldom lethal of itself although its share in predisposing to septic infection is undoubtedly important.

Toxic symptoms are not so easy to separate from the others. There are two groups, those due to the destruction of lymphocytes and those due to actual infection by micro-organisms. The latter also occurs in myelæmia and is there dealt with.

The toxic effects of the disease are best seen in those very acute cases which only live three or four days after the apparent onset of the disease. In these there may be considerable pyrexia and the whole appearance of the patient is that of profound toxæmia. It is true that we are not in a position to positively assert that this toxæmic effect is due to the excessive number of circulating lymphocytes but the latter has various recommendations as a working theory. In any case it is well to provide for their free excretion as far as attention to the amount of urine and regulation of the bowels will allow. It is especially to be remembered that X-rays should be very carefully applied to the spleen if that be enlarged since the effect may be harmful to its activity in dealing with breaking-down lymphocytes. This problem is one that is more to be remembered in cases of myelæmia but even so it should not be forgotten that the spleen may be subject to massive enlargement even in lymphæmia.

Besides the destruction of lymphocytes there is a certain amount of destruction of red cells and this may also give rise to toxic symptoms.

Fever.—This is variable. In the acute cases it is commonly present and may reach as high as 103° F. Less often but still not very uncommonly in children it may amount to 105° F.

or more and this degree of fever is naturally a bad sign. In the chronic cases there is usually no serious amount of pyrexia but close attention to the point such as can only as a rule be obtained in hospital will reveal some slight variations in temperature from time to time. These do not correspond to any definite type and a continuously elevated temperature would give rise to suspicion of complications of a septic nature or might herald a change for the worse in the patient's condition. The regular relapsing fever of Hodgkin's disease is not met with nor does increased pyrexia as a rule accompany changes in size of the glands as may be the case in the latter condition.

Septic complications may give rise to alterations in the temperature varying according to the nature of the infection.

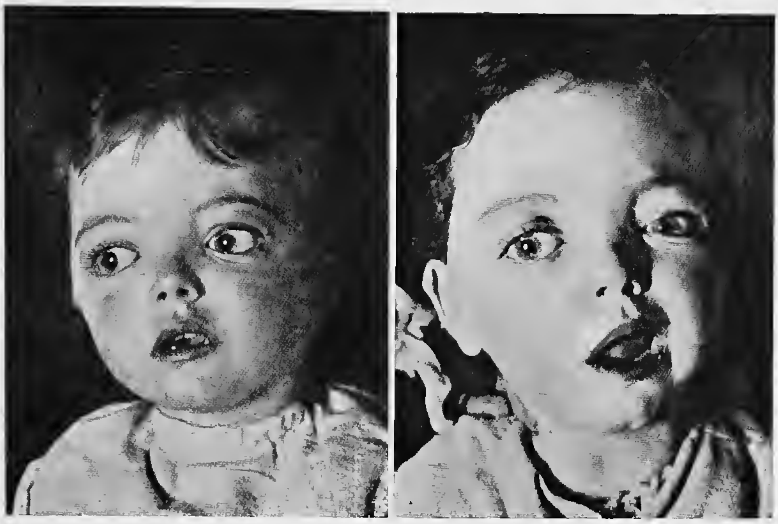
Nervous System.—This is seldom affected to any marked extent unless there are lymphoid growths in the skull and these are very rare in the practice of any individual although the literature contains two or three hundred cases besides, no doubt, many recorded under names which prevent their ready identification. There must also be a considerable number of cases unrecorded.

Among the more common symptoms headache is one of the most frequent and is not confined to the later stages in which it could be reasonably ascribed to the anæmia.

Pain may be due to pressure on nerves following the enlargement of glands or to similar pressure from growths. The author has seen a case in which the first symptom was pain referred to the anal region and sciatica is not very uncommonly complained of when tumours of the pelvic bones are present. When the spleen is enlarged a dull aching pain with occasional exacerbations in which very acute pain may be present is to be expected.

Tenderness may be present on percussion of the bones but this is much more frequent in myelæmia. A general tenderness similar to that met with in scurvy may also be met with in children.

Disturbances of peripheral sensation are uncommon and never very decided unless there is some gross structural lesion such as hæmorrhage or tumour formation underlying them.



Figs. 6 and 7.—Photographs from a case of lymphæmia. The left hand shews the face in repose, the right when the child is laughing. This brings out the paralysis of the right facial nerve—a common feature of leukæmia with skull nodules. (By kind permission of Dr. H. de Havilland Hall.)

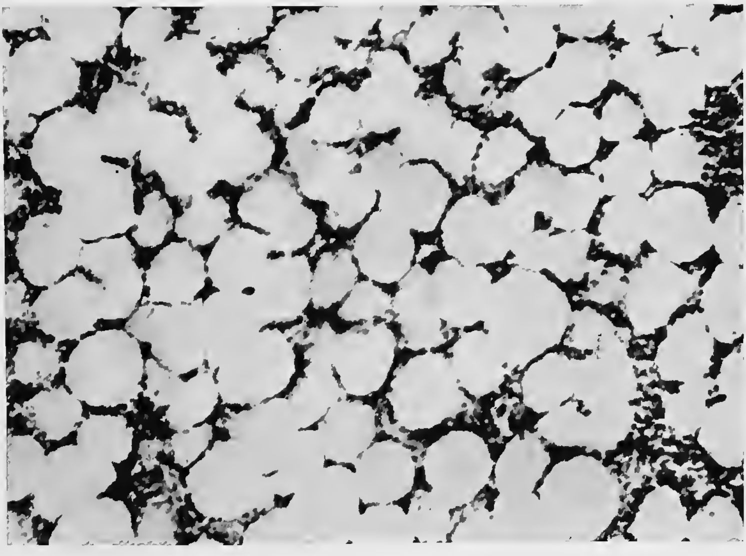


Fig. 8.—Fatty or yellow marrow from the shaft of the femur in a case of lymphæmia. The cell-forming tissue is spreading in between the fat cells which are eventually absorbed, leaving only dense cell-forming tissue. This was the case in the lower end of the femur.

Neurasthenia is not more common in this than in other morbid conditions.

Insanity or rather disturbances which, if persistent, would necessitate institutional treatment are not rare but are usually of short duration and immediately precede death. Of these a condition of confusion and motor agitation is less common than a more or less stuporose state. Only in a few cases has the patient had to be removed to an asylum. Such symptoms are not at all uncommon in severe anæmias, perhaps especially in the Addisonian type and their exact explanation in view of their apparently capricious incidence is not very simple.

So far as the writer is aware there is no case recorded in which the symptoms of combined sclerosis (see page 239) were present but no doubt such cases have occurred and will eventually be recognized.

Special Senses.—Hearing is not very uncommonly affected in the acute cases and this may be due to infiltration of the lining membrane of the ear with lymphoid tissue or to hæmorrhage or to both. This has been especially studied in myelæmia and is there more fully referred to (see page 93). Septic processes in the ears are not uncommon in acute cases when the mouth is in a very bad condition but are practically unknown in chronic cases. Here as in other instances the symptoms recorded are chiefly those of the acute condition not because this is more common—although this may be the case—but because the chronic condition is relatively free from symptoms until its termination when the symptoms are those of the acute cases.

Hæmorrhage from the ear has been recorded. Sight is more frequently interfered with than hearing, corresponding to the more frequent implication of the organs of vision. Optic neuritis may be present even when there are no skull tumours.

The most characteristic appearance although by no means a constant one is that known as leukæmic retinitis. This is the name given to a condition in which white dots and streaks are seen especially along the courses of vessels. The additional presence of hæmorrhages may give an appearance of flames on the retina. Leukæmic retinitis no doubt depends on the presence of infiltration round the vessels of the same nature as that met with in the liver (*q.v.*, page 74). Hæmorrhages alone are not uncommon if the anæmia be severe but are less constant than is the case in Addisonian anæmia. Pallor of the vessels is of course common and by no means peculiar to this disease.

Grosser changes in the retina may be produced by tumour formation pressing on the optic nerve and causing atrophy or by actual invasion of the eyeball by leukæmic tumours.

Sloughing of the whole eye and panophthalmitis may occur when the tumour formation affects the orbit, as is not uncommon in the class of case to which the name chloroma has been applied (see page 88).

The commonest affection of the conjunctivæ is a mild degree of inflammation but hæmorrhages are also very common in the later stages. Trophic changes of course follow excessive protrusion of the eye. Actual lymphoid nodules under the conjunctiva are very rare but nevertheless two or three such cases are on record.

Similar tumours may arise in the eyelids apart from any orbital growth and œdema of the eyelids is common.

The lachrymal glands may also be mentioned here. They are not often affected but when they are, especially if this be the first or most prominent sign of the disease, diagnosis may easily go astray. They may be affected as part of a syndrome to which the name of Mikulicz has been applied. This is more fully dealt with on page 79 and forms one of the most striking of what may be called the accessory syndromes of leukæmia.

The nose may exceptionally be the seat of lymphoid proliferation and the sense of smell may then be lost, but this is not a symptom which is at all likely to dominate the clinical picture. The nose may share in the general sepsis which is apt to supervene in acute cases and toward the termination of the more chronic.

Epistaxis is common. Oozing from the nose of a little blood—hardly sufficient to justify the term epistaxis—may accompany septic processes.

Circulatory System.—Disturbances of this system are hardly such as call for detailed comment. In so far as they are due to fatty degeneration of the heart and vessels they do not differ from those met with in other cases of anæmia and are elsewhere described.

The presence of growths on the ribs or vertebræ or of enlargement of the mediastinal glands or of the thymus may cause abnormalities in the circulation but these are not common.

Hæmorrhages are common and are probably due to fatty changes in the vessels.

Syncope is a possible and not very rare termination of the disease but this is not unexpected when it occurs and is not met with in chronic cases.

An hæmophilic tendency is often seen, *i.e.*, the blood continues to ooze from a prick or small wound for an abnormally long time. This may be met with when there is very little anæmia and no sign of purpura or other hæmorrhage. For this reason removal of a gland should be the last method of diagnosis resorted to if the possibility of lymphæmia has to be considered. In a few cases such ill-advised operations have been the immediate cause of death in patients who would no doubt otherwise have lived at least for a few months and perhaps for years. At the same time it must be admitted that there are far more cases in which similar operations have not been attended by any bad results.

Marrow.—This is hypertrophied in the great majority of cases but not in all. The yellow and normally inactive marrow is encroached upon by active marrow. The latter usually appears red to the eye in spite of the fact that it is largely composed of lymphocytes. It may, however, be of almost any colour varying from a dull grey or dirty yellow to olive green or even bright pea green.

These alterations of colour do not necessarily involve all the marrow but may appear as coloured nodules scattered through the substance of normally coloured marrow.

Gelatinous marrow is also met with but is rather rare. It is more commonly met with in atrophic anæmias (see page 191).

The overgrowth of the marrow often causes some absorption of the cancellous structures and this may be so much the case that it is possible to strip out the greater part of the marrow in a capsule of endosteum. It does not transgress the boundaries of the bones and when tumours are met with they are found to be connected with the periosteum of the bone and not to be due to any spread through the bone itself.

Microscopically the marrow is found to be composed of the same cells that are found in the blood or rather of similar cells. In addition there are nucleated red cells but these are usually relatively infrequent, thus again reflecting the condition found in the blood. Giant cells are also infrequent, in fact, the greater part of the marrow seems to be wholly devoted to the formation of lymphocytes.

The vessels are usually very full, the excessive activity of the marrow naturally being associated with congestion.

When the marrow is green one may find green granules in the cells and even in other cases it is not uncommon to find granules of lesser size but nevertheless quite abnormal and not having any obvious connection with the granules commonly found in myelocytes.

Signs of blood destruction in the shape of pigment granules are not often seen.

The difficulty of examining every bone in the body has made it impossible to say whether all bones are commonly affected alike but it is certain that this is not necessarily the case.

The centres of ossification which may still be present if the patient is a child show the same appearances as the marrow in other situations.

The Blood.—In the early stages there may be little or no diminution in the number of red cells; in fact, these may be distinctly above normal in chronic cases. But even when the number of red cells is high it is usually possible to find one or two nucleated red cells and a few which show polychromasia (page 244).

If the white cells do not show any very definite variation from the normal and the diagnosis seems in consequence to be a little doubtful the presence of even one nucleated red cell in a film has considerable significance. It is sometimes supposed that a nucleated cell may find its way into the peripheral circulation, as it were by accident, even in health. This is certainly not the case.

In a case, then, that was clinically either Hodgkin's disease or lymphæmia and in which the red cells were present in normal numbers the presence of a single nucleated red cell would tell in favour of lymphæmia.

As the disease progresses the anæmia becomes more marked. This is shown by a diminished number of red cells and, at first, by a diminished amount of hæmoglobin in each of them. Later the amount of hæmoglobin in each may be above normal and the blood may present all the appearances seen most typically in Addisonian anæmia.

Nevertheless, nucleated red cells are never so numerous as is commonly the case in myelæmia unless during a "blood crisis" (see page 183) and even then there are seldom more than 2 per cent. of megaloblasts while in myelæmia 10 per cent. is a more usual figure. This is probably due to the fact that in myelæmia the red-cell-forming portions of the marrow are as much involved as the white cell parts and therefore give rise to a considerable number of unusual forms in the blood stream, while in lymphæmia the only affection of the red-cell-forming parts is a physical one, viz., crowding out by the excess of white cells.

As already mentioned the condition known as blood crisis may be met with in this as in many other diseases of the blood-forming organs.

The white corpuscles in the great majority of cases are abnormal either in numbers or nature—commonly in both.

The cell which is more or less typical (and whether more or less is subject to difference of opinion, so that granted the presence of leukæmia of some sort it is often well to rely on the clinical signs for a more exact diagnosis rather than on the blood examination) of the disease varies very much in size and staining reactions. This is not very surprising when we remember that at any given time there are sure to be in the blood cells of very various ages and of very various positions in the evolutionary scale. It is not to be expected that all of these should stain alike.

The sort of cell most commonly met with, although not necessarily forming a majority of the cells present, is very similar to the ordinary or hæmic lymphocyte. This cell it will be remembered has a small round darkly staining nucleus and a relatively narrow rim of lightly staining protoplasm. The protoplasm may be seen to be slightly reticular and on some occasions to contain a few well-marked granules.

In lymphæmia this cell is also found but there are a great number of variants on it, *e.g.*, there may be a kidney-shaped instead of a round nucleus and it may stain less deeply than the protoplasm. Most of the cells are likely to be bigger than the ordinary lymphocyte and the proportion of nucleus to protoplasm is more variable. There may be large granules having the appearance of vacuoles and these vary in size, in the number which may be present in one cell and in frequency in different cases.

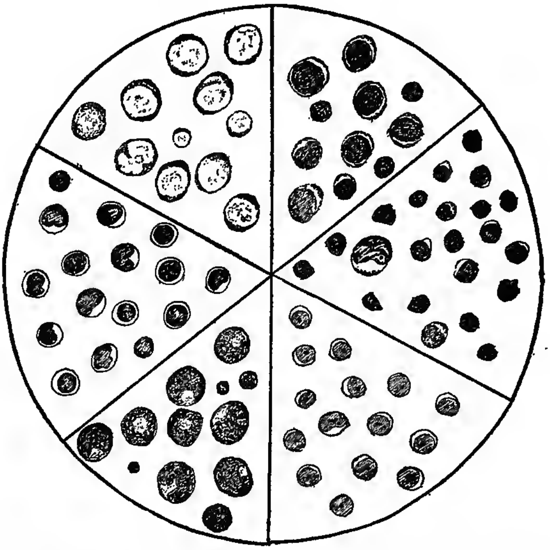


FIG. 9.—*Lymphæmia.* Drawings made from films stained in different ways and from six different cases of lymphatic leukæmia. They show the very different appearances of the cells in different cases and when stained by different methods. The middle section on the left was from a very chronic case, the rest from cases of varying duration, the top one on the left being from a case which was fatal in a few weeks.

From the above it will be apparent that one cannot define a definite cell and say that it and it alone constitutes the test as to whether the disease in any individual case is lymphæmia.

The reader is referred to the illustrations for an idea of the differences that may be met with. The distinction from myelæmia is impossible in a few acute cases but in the great majority rests on the presence in the latter of a great number of the different sorts of leucocytes, *e.g.*, polymorphs, eosinophils and basophils—these cells not being present in any but a subnormal proportion in lymphæmia.

There are a few varieties in the abnormal cells which ought to be mentioned. It is common to meet with what appears as a faintly stained reticular mass with no definite margin. It resembles basket work. This is not a cell but the remains of a cell, the outer envelope (the envelope is not visible but the outer layer of the protoplasm in all blood cells does in fact act as an envelope) has burst and the nucleus has in consequence been enabled to spread out and forms the basket-like mass. Sometimes, especially in the eosinophil cells of normal blood, there are a few granules near and these may enable one to say what sort of cell it was but it is better to disregard these cells when doing a differential count.

Other cells may exhibit protoplasmic processes appearing as a rule as small buds from the periphery of the cell. These buds may become detached and be found free in other parts of the film. They are then likely to be confounded with platelets—it is of no consequence if they are—but they ought not to be counted as cells.

Other cells show mitosis and in these the various stages may all be met with and form a very interesting study. If a cell other than a nucleated red cell is found in any film to be undergoing mitosis there can be no doubt that a case of leukæmia is being dealt with. The other features of the blood examination do not affect this deduction except in the rarest possible cases, *e.g.*, intravascular cyto-phagocytosis and infective lymphocytosis (see pages 276 and 304).

The cases in which it is not possible to come to a conclusion as to whether one is dealing with lymphæmia or myelæmia are rare and as a rule in such cases the exact diagnosis is of no practical importance. These are usually acute cases and the treatment is the same in both diseases and the prognosis equally depressing.

The number of white cells has not yet been mentioned and this is because it is of less importance than might be supposed, in fact, than is generally supposed. When we remember that the number may fluctuate from hour to hour, may be normal for long periods or may never rise to more than a few thousands above the normal, we see that mere numbers are little worthy of reliance. It is quite wrong to talk of a slight degree of leukæmia or of "leukæmia not very well marked" for either there is leukæmia or there is not and the actual numbers of the cells are of no importance in this respect. If there is distinctly leukæmia (in the sense of an increase of abnormal cells in the blood stream other than red cells and not to be explained as the accompaniment of some such change as inflammatory leucocytosis) then the disease Leukæmia (with a large "L") is present and suggestions such as sarcomatosis or, in fact, any other diagnosis is ipso facto out of court.

On the other hand the absence of the symptom leukæmia does not exclude the disease Leukæmia since there may be phases during which the blood appears normal. Since it is a well-known fact that there may be remissions during which the patient returns to normal and even robust health it is hardly surprising that the blood should do the same. This may also happen during some septic infection but the blood then instead of being normal may show the characteristic leucocytosis of sepsis.

As a matter of fact the numbers of cells are usually between 50,000 and 300,000 when the patient is first seen, although they may fall very much lower toward the end. Of these from 50 per cent. to 99.5 per cent. will commonly be abnormal cells, the others existing in more or less normal numbers per c.m.m. (unless there is considerable involvement of the marrow, which is often the case), but in an altered proportion. The higher percentages are most common and a percentage as low as 50 rather rare.

The alterations if any in the number of platelets have not been worked out. The writer is under the impression that they are as a rule very much decreased as far as may be judged from films alone.

Spleen.—This is probably always enlarged but the increase in size may be very slight in some cases. In the chronic cases it is commonly negligible and can perhaps only be made out by percussion. In the acute cases it is larger and can be felt a finger's breadth or so below the costal margin. If death does not soon occur the enlargement may progress rapidly and the typical massive splenomegaly of myelæmia, cholæmia and erythræmia may be seen.

This great degree of enlargement is not very often seen but quite frequently enough to justify its mention, more especially since it is sometimes a cause of confusion between lymphæmia and myelæmia.

The spleen preserves its shape and the notch in the anterior border can frequently be felt.

It is subject to attacks of perisplenitis and the patient may experience a variety of symptoms referable to it. These are dealt with under myelæmia (on page 97) in which disorder they also occur. It is not very often that the acuter troubles such as paroxysmal attacks of vomiting, etc., occur but dull aching pain and some gastric disturbance usually accompany any excessive enlargement.

Post mortem the spleen varies as it does during life as regards its size. If small the consistence is often soft but large spleens are usually hard and on section often contain excess of fibrous supporting tissue. Otherwise the microscopical changes consist chiefly in congestion of the pulp and enormous exaggeration of the cell-forming activity. The malpighian corpuscles do not stand out clearly and their outlines are obscured by proliferation of their constituent cells. The boundaries of their different zones are similarly obscured.

There is also commonly a proliferation of the endothelial cells and signs in them of increased phagocytic activity.

If there have been attacks of acute perisplenitis during life, and occasionally if there have not, there may a good deal of perisplenitis shown by deposits of fibrin on the capsule, thickening and adhesions to the diaphragm and neighbouring structures.

Lymphatic System.—The outstanding feature in connection with this system is enlargement of the glands. Those in parts of the body accessible to examination seem to be more generally enlarged than others and of the more concealed glands only the mesenteric can as a rule be relied on to show enlargement.

There is not a primary implication of one set of glands followed in due course by affection of others as is frequently the case in lymphadenoma but the enlargement is generalised from the first. It is true that it is not invariably so but it affords a good working rule and an aid in the differential diagnosis between lymphæmia and Hodgkin's disease.

Enlargement of the glands in the neck is often the first to attract the attention of the patient since from their position they very soon cause inconvenience. On examination the physician will often discover some enlargement of the inguinal glands also and perhaps a small degree of splenomegaly.

In quite a considerable number of cases the swelling of the glands is only apparent on palpation and in these cases a diagnosis may be very difficult. The writer recently saw a case in which the only sign of illness from the patient's point of view was pain in the right iliac fossa and little else was noted at the first examination except that the temperature was elevated. There was, however, slight stomatitis. Naturally any diagnosis but lymphæmia suggested itself and even the discovery of a few glands just palpable in the neck did not assist a great deal. A blood examination undertaken in the hope that it might afford some help settled the diagnosis. Later there was more considerable enlargement of the glands and the abdominal pain disappeared but even at this time no enlargement was obvious to the eye.

The swelling of glands does not, as a rule, persist without various changes in size and consistency on the part of individual groups. The more usual condition is not associated with very great enlargement of any one gland although a moderate enlargement of each gland in a group may cause a considerable swelling which will sometimes stand out like a hen's egg under the skin.

Much the same variations are seen in the widespread glandular affection occasionally met with in tuberculosis.

Rapid variations in the size of the glands are met with at times; the whole visible swelling may subside in a day or two and reappear in as short a period. This rapid alternation may as is the case in Hodgkin's disease be accompanied by sudden improvement or unfavourable change in the patient's general condition.

The glands are as a matter of fact usually discrete since there is no periglandular inflammation to bind them together but it must be remembered that the fibrous tissue around the glands may as easily be the site of leukæmic infiltration as that in any other part of the body so that a certain amount of matting together can and—although rarely—does occur. This has sometimes led to the diagnosis of lympho-sarcoma, the infiltration being mistaken for actual spread through the capsule of the gland. The latter does not occur.

The consistence of the glands is very variable but the extreme hardness sometimes met with in Hodgkin's disease is not at all common and a soft putty-like feel is the rule.

Suppuration is the exception but in the acute cases in which there is considerable oral sepsis it may be met with. Some degree of redness and tenderness of the overlying skin without actual suppuration is not uncommon.

In one case the glands are said to have discharged lymph through the skin.

Not only does the lymphoid tissue in the glands enlarge but also that in other parts of the body. This is notably the case in the alimentary tract and the various lesions which result are dealt with under that heading (page 71).

In whatever position occurring the histological appearances afforded by the hypertrophied lymph tissues are similar. There is a loss of differentiation of the zones normally observed in a gland and the germ centres may be lost among the masses of cells. As a rule, any definite structure is difficult to make out

Osseous System.—The bones in lymphæmia may be tender on percussion or there may be actual subjective sensations of pain. Neither is common, the latter being least often met with. There are no outgrowths from bone such as are met with in secondary cancerous conditions and in multiple myeloma (page 134). In the usual form of lymphæmia the osseous system calls for no further comment. In the nodular variety the osseous manifestations are very prominent.

In nodular leukæmia—which, of course, is a purely clinical variety—periosteal growths are met with. The genesis of these and similar but non-osseous growths in other parts of the body has already been dealt with (see page 50).

They grow invariably from the periosteum and affect for choice the bones of the head. It must not be supposed that they affect only the skull bones; this is not the case, but if there are any bony growths the probability is that they will affect the skull or be accompanied by growths in that position.

After the skull the ribs and vertebræ and the sternum are perhaps most frequently affected but no bone is exempt. Those which most commonly escape are the bones of the face and the scapula and the bones of the forearm and hands and feet. The long bones such as the femur and tibia are sometimes surrounded by a sheath of marrow tissue, in lymphæmia, lymphoid tissue, which is not definitely increased at any one spot so as to form a tumour appreciable clinically.

These periosteal deposits seem especially liable to be of a green colour and occur chiefly if not entirely in acute cases. A case of myelæmia is recorded in which the skull growths were of sufficient duration to be called chronic and were moreover of a green colour but the writer does not know of any similar case of lymphæmia. In the literature these cases are almost always reported as chloroma (see page 88).

The deposits may reach a large size and are multiple. As a rule they are fairly well circumscribed as far as can be discovered on clinical examination but microscopically there is never a definite capsule except that consisting of the outer layers of the periosteum.

The symptoms resulting from these growths are of enormous variety and only the more frequent can be mentioned. Of

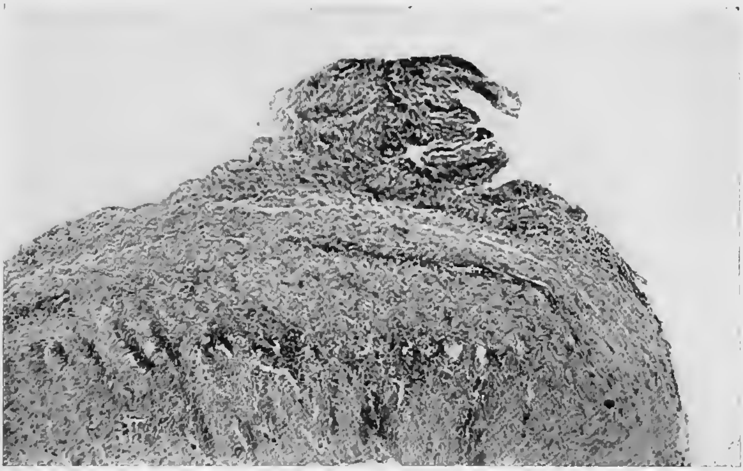


Fig. 10.—Microphotograph of a section of the dura mater from a case of leukæmia. It shews a leukæmic outgrowth of irregular form. The subjacent tissue is infiltrated to some extent with cells similar to those found in the blood. Fig. 11 shews a portion of this tissue under a higher power.

tion those common to the various sorts of anæmia and those associated with terminal infections.

The anæmia produces a certain degree of breathlessness and probably weakens the defensive forces of the lungs. The terminal affection of the lung which one has chiefly to note is broncho-pneumonia. It is seldom that this is quite absent at the time of death. True lobar pneumonia is a very rare complication.

There are not infrequently small areas of lymphoid overgrowth in the lungs and, post mortem, these may stand out as definite white areas but as a rule they are too small to give rise to signs or symptoms distinguishable from those of broncho-pneumonia.

The histology of the lung may present a very remarkable picture for the vessels are full of lymphocytes while the alveoli contain only polymorphs and fibrin. This is only one example of the general rule that the abnormal cells in lymphæmia take no obvious part in the defence of the body against infection and are never met with in abscesses or other collections of pus.

The exception above noted is the train of symptoms which may follow enlargement of the mediastinal glands or of the thymus. Those due to the latter are dealt with when discussing "thymus death" in relation to lymphatism (*q.v.*, page 148).

The writer remembers seeing a case of lymphæmia which was admitted to a chest hospital with a provisional diagnosis of asthma—this having been the complaint of the patient. The fact illustrates the difficulty in diagnosis which may arise when enlargement of mediastinal glands is the first sign of lymphæmia. In this case there was spasmodic dyspnœa, in others a persistent dyspnœa has been seen and has even proved the immediate cause of death. In still other cases cyanosis has been a marked feature and has naturally tended to obscure the anæmia when that has been present in an otherwise easily recognisable degree.

Displacement of the thoracic viscera and consequent impairment of the full activity of the heart and lungs has also been present in some cases. There is, in fact, hardly any symptom of mediastinal tumour which has not been recorded. Hydrothorax is perhaps less frequent in lymphæmia than in other classes of thoracic tumour. If it is present and the fluid be drawn off and examined it may perhaps be possible to identify the cells found with those in the blood but this will not often be the case as the cells undergo various alterations in the pleural exudate and are moreover very similar to those met with in sarcoma of the pleura and similar conditions.

X-rays would probably assist to the extent of strongly suggesting glandular enlargement as against cyst, etc., and continual applications would probably reduce the size of the growth if the patient had not had treatment by this means previously. The X-rays tend to be less successful on a second than on the first occasion of their use.

Alimentary System.—The most prominent symptom here is undoubtedly the state of the mouth. The more acute the case the worse this is but one must not be understood to imply that an acute case must necessarily suffer from stomatitis.

Clinically there is almost always (speaking of acute cases of the most serious variety—those with a "fulminating" course) some swelling of the gums, and this may proceed to the extent of covering the teeth entirely. In such a case the enlargement would no doubt be largely due to lymphoid hyperplasia, the gums and all the oro-pharynx being rich in lymph tissue. In these as well as in less severe cases there is superadded to the lymphoid growth œdema and swelling of septic origin. The lymphoid tissue is very poorly supplied with vessels and is moreover soft so that it frequently ulcerates from the small traumata which it is impossible to avoid in the mouth. As organisms are always at hand there is no barrier to the speedy development of a considerable degree of septic trouble.

In the absence of septic trouble the mouth may at first sight appear normal but closer inspection will often, even in the chronic and sub-acute cases, reveal signs of the disease in the shape of small slightly elevated white areas which are as a matter of fact hypertrophied lymph follicles. These are best seen on the gums but may be met with anywhere in the mouth.

Hæmorrhage from the gums and especially round the tooth sockets is frequent in acute cases in the form of oozing but anything like profuse hæmorrhage is not common. In chronic cases the oozing from the gums is seldom met with except of course at the termination of the disease. In a few cases the disease after a comparatively acute onset with hæmorrhage quietens down and shows no further hæmorrhages perhaps for years.

The lymphoid tissue at the base of the tongue, the tonsils and even the epiglottis may be the site of considerable enlargement and may even cause severe symptoms. Dyspnœa both from hypertrophy of the tonsils and enormous overgrowth of the epiglottis has been recorded in quite a number of cases. In a few this growth has been of the bright green colour of "chloroma."

Of the various post-oral tissues those at the base of the tongue are less often enlarged by conditions other than leukæmia or lymphatism than the remainder and are consequently more useful from the diagnostic point of view.

Symptoms referable to the stomach are not as a rule such as to excite attention or give cause for anxiety but in rare cases the lymphoid overgrowth which may occur is productive of severe signs. This overgrowth may be so extensive as to cause a large tumour appreciable clinically. Vomiting is not uncommon but is seldom persistent or troublesome. Hæmatemesis sometimes occurs.

Paroxysms of vomiting may occur in connection with perisplenitis; these are dealt with when the disorders associated with a large spleen per se are discussed, *i.e.*, under myelæmia on page 97.

Pain referred to the upper part of the abdomen is sometimes met with in the same condition but may also be symptomatic of a tumour of the stomach.

Post mortem such tumour formations in the stomach are seen to be confined to the submucous tissue and never invade the peritoneal covering. The appearance is sometimes that of a mass of small tumours spread all over the stomach and sometimes that of a more diffuse and even thickening, most obvious when the growth is cut into. Even when the naked eye detects no such change (that is, in the vast majority of cases) the microscope will often show some lymphoid overgrowth.

Exactly parallel growths may be seen in the intestine but are less common. In some cases these have ulcerated and there has been persistent diarrhœa. In others diarrhœa has been a symptom of some gravity without any growths being found post mortem. The writer has seen both intractable constipation and equally intractable diarrhœa in sub-acute cases of lymphæmia.

Rarely tumour formation of the gut has been so pronounced as to give rise to a tumour detected during life and it has even led to laparotomy. These cases are especially instructive from the point of view of diagnosis. In one of the recorded cases there was a palpable tumour in the appendix region with pain, tenderness and pyrexia. The patient was operated upon and died shortly after the operation. The condition found was undoubtedly appendicitis but it was due to extensive involvement of the appendix and the surrounding tissues in lymphoid growth. A blood examination had been made but unfortunately a differential count had not been done at the time of operation; a total white cell count of seven or eight times the normal having been regarded as sufficiently confirmatory of the clinical diagnosis of pus formation. There is no particular reason, as it happens, to suppose that the patient's death was hastened by the operation in this case but it illustrates the difficulties which may arise very well. In another case the presence of considerable pyrexia and an indefinite tumour of the abdomen gave rise to the diagnosis of hepatic abscess and this was considered the most probable explanation of the physical signs and symptoms by several physicians. Laparotomy was performed and revealed enlarged glands only and soon after a diagnosis of lymphæmia was made from a blood examination. In this case the operation had no evil effect as far as could be ascertained although the patient died before very long as, indeed, the high pyrexia would have led one to expect would be the case. In some cases, however, operation for the removal, for example, of a skin tumour or a gland for histological examination has been followed by death from hæmorrhage. This has been the case even in chronic cases in what appeared to be a very fair state of general health so that operations may be considered definitely contra-indicated in leukæmia.

Melæna is not particularly common but has been present in some cases. A diagnosis of typhoid has been made in a few cases; in one that the writer had the opportunity of seeing it was negatived both by the negative Widal reaction and the positive finding of abnormal cells in the blood but without a blood examination the diagnosis was certainly fully justified in the circumstances.

This type of difficulty is far more commonly encountered than that due to actual tumour formation. It may be mentioned that among the first diagnoses made in cases of lymphæmia both with and without tumour formation the author has met with the following, viz., mumps, septic stomatitis, asthma, typhoid, rickets, mediastinal sarcoma, hysteria and sciatica. It is obvious that some of these only narrowly missed the truth; in the literature of the subject there are numerous such examples so that lymphæmia is not so easy a disease to diagnose as one might think would be the case.

The Liver.—This is usually slightly enlarged but may be very markedly so. The latter abnormality is more frequently met with in myelæmia. Post mortem it varies a good deal in tint and this depends on the degree of congestion, of anæmia and of fatty change.

Microscopically this is one of the most important organs to examine if the diagnosis is in doubt. The sign which the liver affords and which is for all practical purposes pathognomonic of leukæmia (although it will not necessarily tell us which variety) consists in the presence of cellular infiltration of the structures which are carried in Glisson's capsule. Thus the vessels and the bile ducts are surrounded by a small round-cell infiltration and this often extends to the smallest ramifications so that the whole liver tissue seems to be infiltrated with cells similar to those met with in the blood (allowing for the difference in preparation of the tissues in the two cases). In places there may be definite tumour formations and these

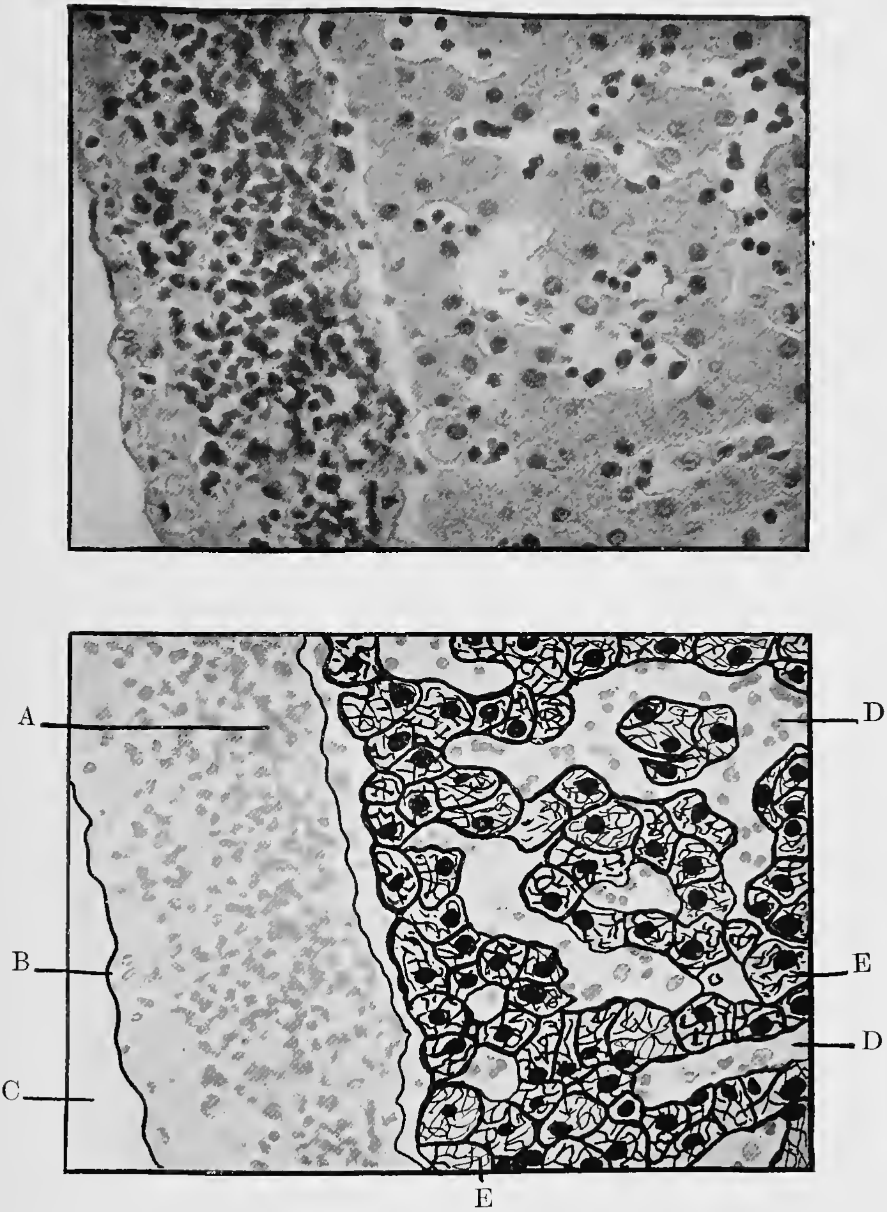


Fig. 12.—Photograph under a high power of the liver in a case of leukæmia. The lower figure is a diagram of the upper. It shews on the extreme left (*C*) the lumen of a vessel, next to this the lining epithelium (*B*) of the vessel and the perivascular leukæmic growth (*A*). On the right are seen the cells of the liver (*E*) which are normal and the intervening capillaries (*D*) which are laden with leucocytes. This photograph shews the typical condition of the liver in leukæmia, a condition more nearly pathognomonic of the disease than any blood condition.

may be seen by the eye as white patches on the surface of the liver. Very rarely they project from the surface.

Symptoms referable to the enlargement of the liver are rare in lymphæmia but are rather less so in myelæmia (see page 102).

The Urogenital System.—In chronic cases there is little or nothing in the way of clinical signs to suggest implication of the kidneys in the morbid processes characteristic of lymphæmia. Nevertheless there is often some microscopical change. This is as elsewhere a cellular infiltration.

In the acute cases the kidneys are almost invariably enlarged and post mortem present a very remarkable and typical appearance. They are irregular in contour and are spotted and splashed with white and red areas of all sizes and shapes. These are due respectively to lymphoid infiltration and to hæmorrhages beneath the capsule. On section the kidney is seen to be especially involved in the infiltrating process but there is no particular localisation of it to any one part of the organ unless it be the calyces. These may show growths of considerable size invading the pelvis and limiting its capacity. It is, of course, in just this part that the fibrous tissue is most dense and lymphoid tissue is found in the same parts in the fœtus.

Various degrees of inflammation of the kidney are also met with and corresponding to this we get albuminuria during life. Fatty changes are also met with.

The presence of enlarged kidneys in a case which was clinically one of, for example, multiple sarcoma of the skin should suggest the probability of leukæmia.

There is nearly always some change in the urine. As already mentioned albuminuria is quite common and casts of various sorts may be met with. Hæmaturia is less common. There is often a copious deposit of urates even when the temperature is not particularly elevated and uric acid is also met with—as an expression of the disordered metabolism due to excessive destruction of lymphocytes.

The urinary deposit besides showing casts may in part consist of cells similar to those found in the blood especially if there are as a matter of fact growths in the pelvis.

There are two rare urinary findings which merit attention. The first is the presence of a green pigment which is characteristic of the chloromatous variety of leukæmia. It is very rare but naturally very striking and characteristic. It may perhaps be mentioned that the use of patent medicines containing methylene blue might give a somewhat similar colouration.

The second abnormality is equally rare and consists in the presence of albumose in the urine or to be more exact the presence of the Bence-Jones body whatever its exact nature may be. This is almost constantly found in multiple myeloma, a disease which will be subsequently discussed (see page 134), but is very rare or very rarely identified in leukæmia. It has only been recorded in some two or three cases. It differs from the ordinary albumen in re-dissolving on heating to a higher temperature than that at which it is precipitated, and in other features which will be subsequently discussed.

That it should be met with in leukæmia is hardly matter for surprise since it is extremely probable that it is directly formed from the products of white-cell destruction.

The testicles are sometimes enlarged and this may even be one of the first abnormalities to be noted. The enlargement is usually symmetrical.

Similarly the ovaries may be affected but the genital glands usually escape. The virility of male and female patients is not affected although the disease exercises a very prejudicial effect on the recovery of the mother after parturition.

Persistent priapism is a feature which has been often remarked and, again, may be the first sign of the disease. Leukæmia is the commonest single cause of this anomaly but the cases are few and far between. It depends on lymphoid infiltration of the penis and this may either be diffuse or more rarely definitely nodular. It rarely passes off but may do so. In some cases it proceeds to destruction of the penis from failure of the blood supply.

Finally one may mention the extraordinary case of chloroma in which the lining membrane of the urethra was enlarged into a homogeneous green mass.

The Skin.—The most frequent abnormality of the integuments

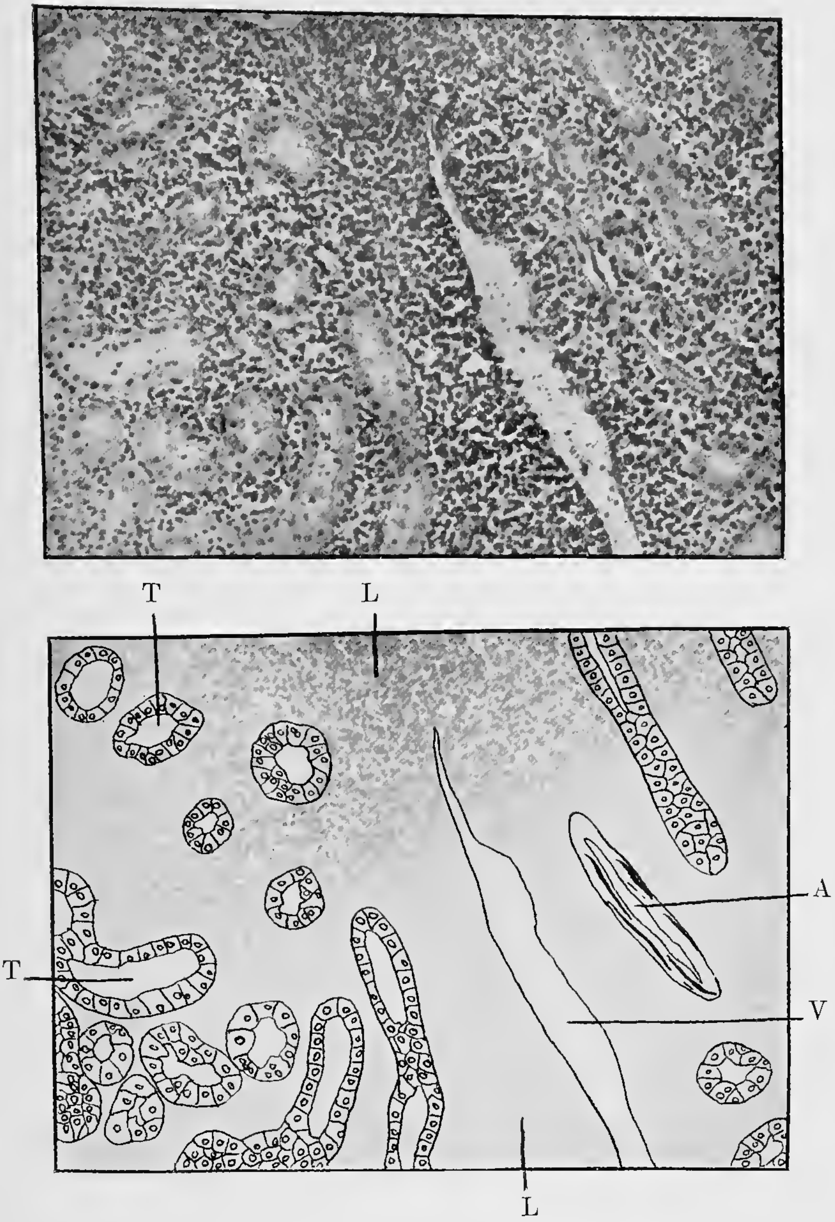


FIG. 13.—Microphotograph of the kidney in a case of acute lymphæmia. The upper photo is untouched, the lower a diagram of the same. *TT*, tubules of the kidney seen in section; *A*, an artery; *V*, a vein; *L*, new growth of hæmopoietic or blood-forming tissue crowding between but not invading the vessels and tubules. The cells of which it is composed are identical with those in the blood. This tissue is to be regarded as growing in situ from primitive mesoblastic cells and not as in any way of the nature of a metastasis or as derived from the cells in the blood. The latter are rather derived from this lymphoid tissue.

is the occurrence of subcutaneous hæmorrhages which may be quite small or large and confluent. The latter are rare and are soon followed by the death of the patient. In any case purpura is a sign of considerable gravity, since it is not common unless the degree of anæmia is severe and the fatty changes in the vessels resulting therefrom considerably advanced.

When hæmorrhages become absorbed there results a greenish tinge which may lead to a diagnosis of chloroma which subsequent events fail to justify. The author has seen three cases diagnosed as chloroma during life and although two of these were eventually proved to be so, feels that the diagnosis is a very risky one to pin one's faith to, *i.e.*, if the colour of the skin is taken as the indication. In one of these cases there was certainly a greenish tinge which corresponded in position to green subcutaneous tumours—it was a dull olive tint.

Various lesions short of tumour formation are met with quite frequently. Some of these, such as ichthyosis, are merely casual associations but others seem to be directly connected with the disease. Evanescent papular lesions sometimes preceded by erythema are most typical. Their histology is not known and consequently little except that they do occur can be said about them. In a very small proportion of cases there has been considerable irritation; this symptom is more often encountered in Hodgkin's disease and is practically constant in a rare disease somewhat closely connected with leukæmia—viz., mycosis fungoides. It there precedes the formation of multiple skin tumours and this may also be the case in the irritation of skin lesions in lymphæmia. The histology of the two diseases is so similar as to be frequently identical to all ordinary tests.

Vesiculation and pustulation are also met with but are not very common. It can hardly be said to what extent they are dependent on the disease process or how far they should be regarded as accidental associations.

Actual tumour formations occur in two forms. In one there is a diffuse change; in the other a more localised affection. The two may co-exist. Either is very rare except in the acute cases when some degree of the diffuse form is fairly common and not very often distinguished from simple œdema. It affects for choice the skin of the face and the scalp and may give rise to great differences of colour in these parts. A purplish or slate colour is rather typical; greenish tints have also been noted. In one case the greenish tint noted during life was not found after death. There may also be an infiltration without obvious alteration of the skin—which is of a waxy hue as a rule in the later stages but may be normal if anæmia has not developed.

Actual tumour formation gives rise to different appearances according to the depth from the surface at which the lymphoid infiltrations commence. Thus all the tumours may be distinctly subcutaneous and cause no alteration of the overlying skin or, on the other hand, there may be no deep tumours but a great number of superficial lesions. These commence as a papule or even as a patch of erythema and may grow with extreme rapidity. Eventually they may reach the size of the closed fist and tumours of this size have been noted on the face causing, of course, great disfigurement. They are usually multiple and the face and trunk are more often affected than the extremities. In a certain number of cases there has been only a single tumour noticed and no others have developed later.

The tumours may vanish with the same rapidity noted in their arrival and may never recur but as a rule do return sooner or later. They are by no means confined to the acute cases (as is true of many of the "associated syndromes" of leukæmia, viz., Mikulicz's disease, chloroma, etc.) and occur as the first manifestations of the disease in a fair number of cases. Confusion with mycosis fungoides and multiple sarcoma of the skin is, in such circumstances, very likely to occur. They exhibit all sorts of tints and a slate colouration is again by way of being typical of the condition.

Both infiltrations and tumours are especially liable to be the seat of hæmorrhages but as bearing on the theory that they are due to growth of cells directly derived from the blood stream it may be noted that they do not occur on the site of pre-existing hæmorrhages as one would expect if this theory were valid. From the same point of view their frequent symmetrical development is noteworthy.

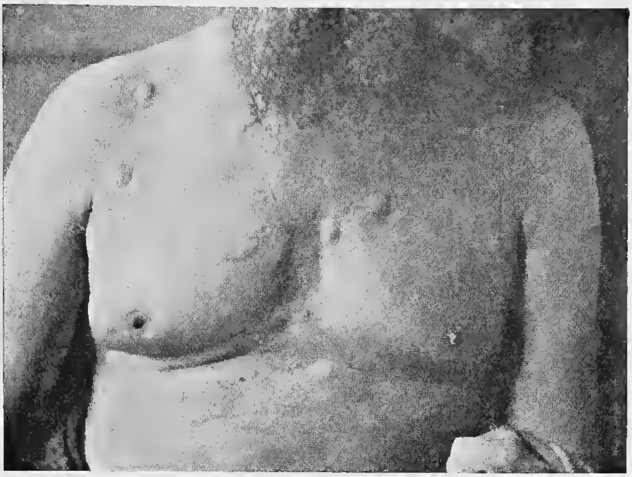


Fig. 14.—Subcutaneous nodules in a case of lymphæmia. (By kind permission of Dr. H. A. Lediard.)

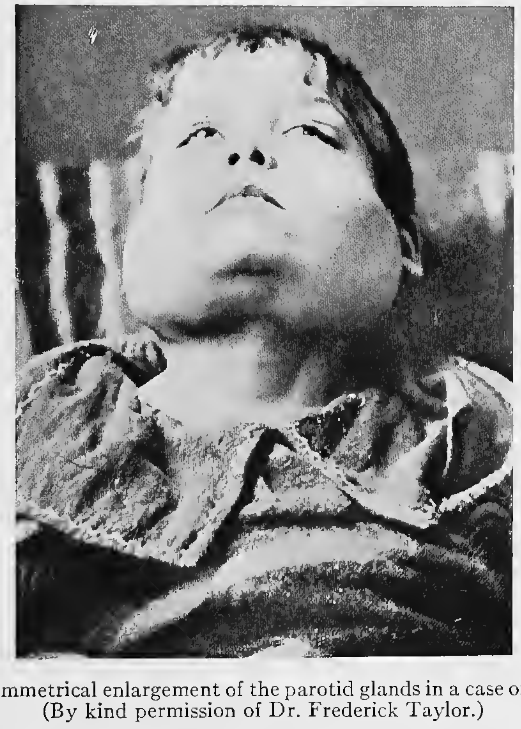


Fig. 15.—Symmetrical enlargement of the parotid glands in a case of lymphæmia. (By kind permission of Dr. Frederick Taylor.)

The general resistance of the skin is often very markedly impaired in leukæmia and this must be borne in mind when any application to the skin is proposed. In at least one case the application of a blister caused rapid and extensive necrosis of the integument. Caution is naturally called for in employing X-rays for this condition.

Glands Other than Lymphatic.—There is a very striking syndrome associated with glandular conditions in leukæmia. This may conveniently be called the symmetrical glandular syndrome and is one of the syndromes associated with leukæmia but occurring also in other conditions. It is in part covered by the undesirable term Mikulicz's disease but this concerns only the glands of the head, *i.e.*, the lachrymals and salivary glands. In leukæmia any pair or pairs of symmetrical glands may be affected with generalised infiltration or nodular thickenings. The salivary glands and the breasts are perhaps most often affected but the lachrymals, adrenals, ovaries and testes may also be affected. In at least two cases the development of this syndrome has unfortunately resulted in the amputation of both breasts.

It will be noted that this involvement of paired glands is also seen in other diseases and of these mumps is the first that comes to mind. In this the testicles and the parotids are fairly commonly affected and involvement of the lachrymals and the breasts has been recorded.

It may be conjectured that the fibrous tissue in these positions is, as it were, less stable than that in other parts of the body and is so more ready to react to disease and the paired distributions lend some countenance to this view. At the same time one can hardly say exactly what "less stable" may mean although it may convey to the mind some not wholly inaccurate idea of the actual state of affairs.

More work of an experimental nature and more clinical observation on this subject would be of great interest.

The effects of these various glandular swellings are many. The enlargement of the lachrymal glands may lead to displacement of the eyeball and to consequent impairment of sight. The implication of the salivary glands will naturally tend to produce xerostomia but as a matter of fact the complaint of dryness of the mouth does not seem to have been a prominent one possibly owing to the partial involvement only of the glands and to the fact that the gland epithelium itself is not affected except by pressure.

The simultaneous swelling of all the salivary glands produces a striking appearance and this is shown (although it is not very marked) in the illustration of "Mikulicz's syndrome" Fig. 15.

The swelling of the breasts may continue for some time before it becomes obvious to the patient. As a rule the skin is not affected but this may be the case.

Swelling of the testes and ovaries has already been mentioned.

Hypertrophy of the adrenals is not very common amongst these rare concomitants of leukæmia and the author is not aware of any case in which it has been suspected during life. Nodules of growth are less uncommon but are still rare enough. The symptoms to be expected would naturally be those of Addison's disease, viz., frequent, low-tension pulse, wasting, vomiting and abdominal pain, lethargy or stupor and perhaps pigmentation.

Metabolism.—Apart from the disorder of metabolism which is necessitated by the removal of excessive numbers of dead lymphocytes there is no very marked disorder. In a few cases, however, there has been extremely rapid wasting without so far as could be ascertained adequate cause. In chronic cases the bodily condition may be excellent and the digestive and secretory organs apparently healthy.

The anæmia which is usual especially in the last stages naturally exercises an unfavourable influence on metabolism.

Course.—This is extremely variable, so much so that there is the greatest difficulty in giving a prognosis in any but the acute cases. Those cases in which the first signs of the disease have been accompanied by fever, stomatitis and purpura are seldom found to survive more than a few months at most—many die within a few weeks and quite a considerable number have proved fatal in less than a week. In one case the patient died within three days of the apparent onset of the illness.

On the other hand there are a few acute cases which have quieted down and have afterward lived for several years. The chronic cases may live for so long that the disease may almost be said to run a benign course; they may eventually die from intercurrent disease without ever having experienced anything like an acute phase of lymphæmia. A duration of ten years is not uncommon and much longer periods of good health may be enjoyed after the disease has declared itself.

Neither in the acute or chronic case does the disease run an uninterrupted course as a rule. There are periods of relatively ill health and periods during which the patient may declare that "he never felt better in his life." Unfortunately these long cases are not very often followed throughout their whole course by the same medical man and in consequence there is some paucity of information as to the exact course of the very chronic cases.

Remissions occur in even the acute cases and these may result in temporary restoration of complete subjective health or only in distinct amelioration of the patient's condition.

They may result from treatment or from intercurrent disease especially if that be of the nature of a septic infection. This aspect of the matter is more fully dealt with under myelæmia in which remissions are also met with and are of a similar nature. (See page 105.)

Toward the end in all cases that run an uncomplicated course a considerable degree of anæmia develops and this undermines the resistance of the body and hastens the fatal termination. Death is often due to the supervention of septic processes either of the lung primarily or in the first place in the mouth or nose or ears. From these there is usually spread a septic form of broncho-pneumonia.

Otherwise death may result from asthenia and heart failure or from hæmorrhage into the brain or meninges. Rare accidents such as rupture of the spleen have been recorded—usually in acute cases with very congested and friable organs. This contrasts with the state of affairs in myelæmia when rupture of the spleen is more usually associated with chronic massive enlargement with fibrosis.

Clinical Varieties.—Of these we must first mention the acute and chronic. They have already been discussed in various places and the terms are sufficiently self-explanatory.

To either the acute or the chronic form one of the other varieties may be added—these varieties are those elsewhere referred to as associated syndromes. They may be grouped together under the title nodular leukæmia. In all the characteristic lesions are dependent on local overgrowths of lymphoid tissue resulting in diffuse thickenings or tumour formation.

The first of these syndromes is that commonly designated chloroma. This is discussed on page 88.

The second is that previously referred to as the symmetrical glandular syndrome—a part of this syndrome is covered by the term Mikulicz's disease. The latter term, however, is unfortunate since it is not a specific disease that one is dealing with but an association of clinical signs met with in more than one morbid condition.

The third associated syndrome has as much title to the name of mycosis fungoides as the second has to that of Mikulicz. It is however a syndrome distinct from that of mycosis although presenting many similarities. The similarities are so considerable that there can be no doubt that confusion has frequently arisen. In this syndrome the presence of skin nodules of a chronic type, liable to sudden disappearances and as sudden revivals, existing in a person who eventually develops severe anæmia and dies therefrom is characteristic.

The only other syndrome which is apparently very distinctive is that associated with persistent priapism.

There remain the various syndromes which may ensue on, for example, the presence of nodules in the intestinal tract or bones but these do not tend to follow one type, striking in character and readily appreciable clinically. These are conveniently referred to as nodular leukæmia with any qualifying description that may seem advisable.

Complications.—These are almost entirely septic in nature. It is true that various other diseases may co-exist but except those of a septic nature few seem to exert any decided influence on the disease or to be particularly prone to occur. It may be especially mentioned that there is no sort of parallel in lymphæmia to the well-known association between tuberculosis and Hodgkin's disease.

The septic infections comprise those due to staphylococci, streptococci, bacillus coli communis and the various organisms which may be found in the mouth. It is often impossible in any particular case to say which of these latter is or is not pathogenic so that one must incriminate all mouth organisms equally. It is a matter for regret that these patients are usually past deriving benefit from vaccine therapy by the time that oral infection becomes severe.

Of the streptococcal disorders erysipelas is one of the best defined but is not at all common. It is commonly responsible when it does occur for a diminution of the circulating lymphocytes and if the patient does not succumb to it may be followed by a distinct improvement in the general condition.

Staphylococcal infections, pure or mixed, are met with in the shape of nasal, aural, conjunctival, buccal and glandular suppuration. The formation of pus in the glands is not so common as one might expect from the prevalence of good cause for the same in the structures which they drain. Why this should be is not explained. Septic pneumonia is usually present toward the end. The author is not aware of any bacteriological investigations of the lungs in such cases but it seems probable that the infection is derived from the mouth and is, therefore, very likely mixed.

Lobar pneumonia due to the pneumococcus is a very rare complication.

Infection with organisms of the coli group is only met with in the immediate neighbourhood of their normal breeding ground —the intestinal tract. They (the organisms) may be found in a virulent condition when there is an ulcerative condition of the enlarged lymphoid follicles in this situation or even in association with peritonitis as in the case of perforation following such ulceration.

At the end of the disease, perhaps a few days before the death of the patient, there is a much more extensive infection of the whole body by various organisms and this terminal infection is a feature of other diseases as well as of lymphæmia. It is probably due to absolute failure of the defensive powers of the body such as one is not surprised to find in a moribund patient with severe blood changes.

Diagnosis.—The most important point, almost the only absolute point, is examination of the blood. This, therefore, should be done in any suspected case. For the purpose of diagnosis a dried film is sufficient; in the majority of cases microscopical examination of a fresh drop of blood will give the diagnosis. In a few cases there may be no change in the blood and then a confident diagnosis will be very difficult if not impossible.

The next most important point in the diagnosis of lymphæmia is the realisation that it may be present in the particular case under notice. When once the possibility of its presence is realised it is possible by fairly simple methods to verify or disprove the tentative diagnosis.

Clinically it resembles a great number of other cases in which there is enlargement of more than one group of lymph glands. Of these tuberculosis is perhaps most commonly met with. Diagnosis rests on blood examination unless some lymphoid hypertrophy can be discovered in the mouth or leukæmic retinitis is present. Both diseases are very apt to be accompanied by anæmia but in neither is it necessarily present.

Hodgkin's disease may present difficulties and these are dealt with on page 126.

The most difficult cases are those which first come under notice for some symptom which one does not readily connect with any blood disease. With reference to these conditions we may recapitulate certain remarks already made, as follows:

That swelling of lymphatic glands without obvious cause should lead one to think of leukæmia. Hypertrophy of other lymphoid tissues especially in adults makes the suggestion of leukæmia very much more forcible. Swelling of small lymphoid follicles on the gums is practically diagnostic of the condition.

That a massive swelling of the spleen most often—in the absence of tropical diseases—means some blood disorder and demands a blood examination.

Multiple sarcoma of the skin, the glands or bone is to be viewed with distrust and no operation of any nature should be undertaken until a blood examination has been made.

Persistent priapism is more often met with in leukæmia than in any other condition.

Mumps is not the only disease which causes symmetrical swelling of the lachrymal and salivary glands. Such swelling is also met with in leukæmia.

The other points in diagnosis have already been dealt with on previous pages and need not here be recapitulated.

Treatment.—The only drug which seems to be of any benefit is arsenic. This may be given in any of the ways mentioned on page 347 and the succeeding pages. In almost all cases Liquor Arsenicalis Hydrochlor. by the mouth is as good as other forms, although vomiting will rather contra-indicate this method when arsenic may, however, be given hypodermically.

X-rays have not been so generally employed as in myelæmia but have the same effect in lymphæmia and in any but the most acute cases will produce improvement. Even in the acutest cases improvement has resulted so that the patient has lived two or three years after the onset of the disease. For details of the X-ray treatment see page 345.

In chronic cases in which the general health is so good that treatment seems superfluous the question of the duty of the physician in this matter arises. There will certainly come a day when an acute phase of the disease appears. Is it possible to prevent this or to postpone it by treatment in the interval? No definite statement as to the proper answer to this question can be made in the present state of our knowledge but it is obvious that to this question any really useful advance in therapy should return a positive answer—an affirmative answer. In the meantime the only indication which appears to the author rational is one that is more and more insisted upon as we get nearer the truth of the etiology of diseases at present obscure. This is to attend to the state of the intestinal tract even as we do in Addisonian anæmia and many other conditions to be subsequently dealt with.

Some of the means applicable to this purpose are mentioned on page 257.

In the acute cases the state of the mouth often affords an indication for immediate symptomatic treatment. A mouth wash should be prescribed for use after every meal and frequent swabbing out of the mouth may be necessary, at least at first. Irritating preparations are to be avoided in all cases. The best general antiseptic for use in the mouth is undoubtedly hydrogen peroxide. The twenty volumes solution usually supplied is calculated to give off twenty volumes of oxygen for every volume of fluid. This is too strong, or rather unnecessarily strong, in most cases and should be diluted to 1 in 4. After the hydrogen peroxide glycothymoline is a pleasant preparation and helps to remove the bitter taste of the former preparation. Patients do not as a rule object to hydrogen peroxide but in many acute cases the patient is too ill to manage a mouth wash of it and it can then be applied on wool swabs. There is considerable effusion of gas and the froth must be carefully washed out of the mouth afterward. Hydrogen peroxide is also of great assistance when there is oozing from the gums as it is an excellent styptic.

Insufflation of iodoform powder may be employed.

When the condition of the gums begins to improve, as it very fortunately does with considerable readiness, some slightly astringent preparation may be employed. Glycerine of tannic acid diluted with equal parts of warm water is here of value.

Rest in bed is of course necessary for the acute cases and should be employed in any case if the red cells fall below 4,000,000 per c.mm. It is of great value as sparing the expenditure of oxygen necessary to keep up the body processes. This is equally true of any anæmia since there is always a deficient oxygen-carrying power when the number of red cells is below normal.

The diet must be such as the patient can best take but highly nitrogenous foods are to be avoided—the patient will make no objection to this. In chronic cases the patient will choose his own diet.

Other questions of treatment must be determined on general lines. Surgical treatment must only be employed to avert immediate danger to life, *i.e.*, pressure of a growth on vital structures. Treatment by radium, X-rays, benzol, etc., is similar to that employed in myelæmia and is dealt with on page 107.

CHAPTER V

CHLOROMA AND MYELÆMIA

CHLOROMA

The syndrome to which the name chloroma has been applied may complicate either variety of leukæmia. The outstanding feature which it presents is a green colouration of the lesions met with and these are apt to take the form of lymphoid nodules on the bones of the skull. With these nodules are associated such clinical signs as exophthalmos and facial paralysis.

The green colour may be found in all the lesions in any individual case or only in a few, it may also vary from a bright pea green to a dull olive tint. Certain of the shades met with are commonly seen in pus from abscesses—in the absence, of course, of the bacillus pyocyaneus.

The nodules on the skull although characteristic of the syndrome of which they are an essential part are also met with in cases of leukæmia in which there is nowhere any trace of a green colouration.

Thus, except for the colour, there is nothing to justify the classification of chloroma as a disease apart—a distinct clinical entity; and the colour is met with in all and every type of leukæmia, in chronic and acute cases alike, sometimes confined to the bone marrow, sometimes seen in only one or two of the enlarged glands and occasionally in the leucocytes centrifuged from the blood or in the blood post mortem.

But in no other diseases except in the two varieties of leukæmia does one meet with this type of periosteal nodule or with this green colour.

There is therefore every reason for supposing that chloroma is merely an associated syndrome of leukæmia and the striking and apparently distinct disease first described in 1823 is seen to be one of the least well defined of disorders and no more a clinical entity than is diarrhœa or purpura.

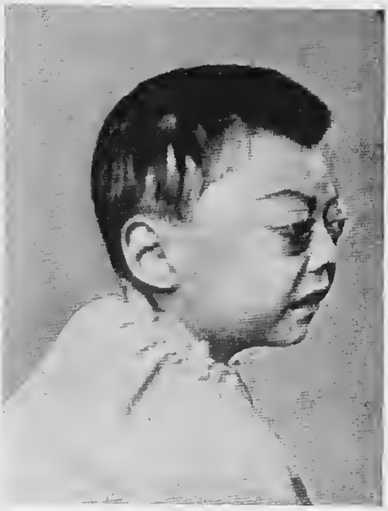


Fig. 16.—Chloroma. (By kind permission of Dr. Melville Dunlop.)

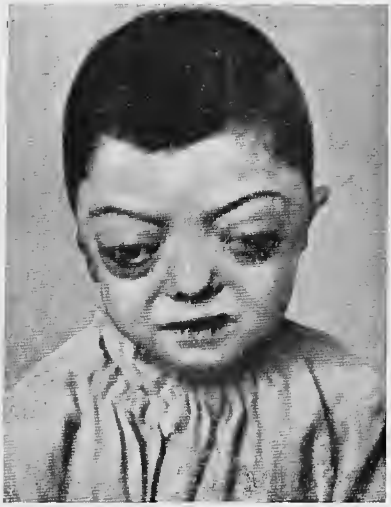


Fig. 17.—Chloroma. (By kind permission of Dr. Melville Dunlop.)

The genesis of the green colour is not known. Byrom Bramwell has recorded the opinion that there are probably cases of chloroma in which there are no tumours and no green colourations. That this apparent paradox is but a statement of the truth there can be no doubt—any case of leukæmia will fall within his definition. It is, however, possible that there is a colourless pigment or one of insufficient intensity to give rise to an obvious green in all cases of leukæmia. This pigment is in the leucocytes and one may hazard the opinion that it is a product of degeneration and moreover especially of the degeneration of immature cells. This would explain the varying shades of colour which are yet connected, the association with leukæmia and especially with acute leukæmia—in which the cells are usually of the more primitive types—the similar colour seen in pus and the presence of colourless granules which has often been noted in the circulating cells of leukæmia.

Unfortunately the colour soon fades and has so far defied chemical analysis. So far as the author is aware there has never been an attempt made to isolate a colouring matter from pus when it shows a greenish tint. This, however, might be a useful step toward solving the difficulties met with in analysing the green colour of chloroma.

The clinical features of chloroma do not differ from those already described under lymphæmia with skull nodules and to be presently described under myelæmia. It is usually associated with the acuter cases of either disorder but chronic cases of two to three years' duration have been reported.

MYELÆMIA

Synonyms.—Spleno-medullary leukæmia or leucocythæmia, splenic leukæmia, myeloid leukæmia, myelocythæmia. Cases have also been reported as pseudo-leukæmia and leukanæmia.

Definition.—An apparently purposeless overgrowth of leucocyte-forming tissues reflected in the blood stream by a varying increase of leucocytes or their forerunners.

Nature.—If lymphæmia is eventually proved to be infective the same etiology will no doubt apply to myelæmia. In the present state of our knowledge we can conjecture but cannot determine.

Many people consider that leukæmia is of the nature of a malignant growth as, for instance, cancer of the stomach is a malignant growth. There are certain objections to this view of which a few may be here briefly summarised. Of any given epithelial tissue there may be 1. Malignant infiltrating hyperplasia, *i.e.*, cancer, in the ordinary acceptance of the term, or 2. Benign new growth, of which papillomata are the type, and 3. Physiological hyperplasia of which the thickening of the epidermis on the hands of a labourer is an example. As regards the marrow we have 1. Sarcoma of the myeloid type and possibly less typical endosteal growths, and 2. Multiple myeloma which disease may be considered to correspond to a benign new growth, and 3. Leucocytosis and polycythæmia which are in the nature of physiological reactions. Here there is no place for leukæmia.

Again there are no metastases in leukæmia; it is true that there are nodules in different parts of the body but these are often symmetrical, do not infiltrate structures in which they do not arise and are certainly not formed from the cells in the blood. Their histology at once removes them from the category of new growths such as sarcoma or carcinoma.

Moreover new growths do not undergo the remissions of leukæmia or, at least, not to anything like the same extent nor do we find cancers of the same structures and as far as we can judge of the same age in so many different places at once as is the case with the lesions of leukæmia.

On the other hand if we assume that leukæmia is of the nature of a reaction to excessive loss of blood cells the facts known fall readily into line.

That there are analogies between cancer and the leukæmias no one will deny but they are not sufficient to bring the two into the same class. It is open to anyone to argue—as has been done—that the stimulus which causes cancer is provided by the preceding destruction of tissue on the site of the new growth. Something the same has been said above of leukæmia but yet the two types of disease are plainly separate. If leukæmia is a "new growth" it has no analogies except those which are here considered under the title of Generalised Affections of the Blood-forming Organs and must, with these, be classed apart as a very distinct type of disease process.

The above remarks are of course more tentative theories than proven facts and the subject is such a wide one that adequate discussion of it here would be quite out of place. It may be remarked finally that if leukæmias are cancers then the metastases of cancer are not due to emboli from a primary growth nor to spread by direct continuity along lymphatics but are primarily formed in each situation in which they occur under the influence of the same stimulus that produced the original tumour. Probably few persons will be prepared to subscribe to this view of the etiology of cancer metastases and consequently will reject the analogy which necessitates it, *i.e.*, that leukæmia is to be regarded as a form of new growth of the bone marrow or glands. However, the theory and the analogy form a fascinating and possibly productive field for discussion and research.

General Pathology.—As in lymphæmia we assume a "stimulus"—the "cause" of the disease—which has a maximum influence on myeloid tissues throughout the body. It appears certain that there are everywhere in the body (excepting epiblastic and hypoblastic structures) and probably in close relation to the capillaries mother cells which have the potentiality of developing into either myeloid or lymphoid tissues. It is the reawakening of these into activity which constitutes the basis of leukæmia. It is possible that these cells are formed in the perivascular lymphatics.

The disease now under discussion has the same general pathology as lymphæmia, the same remissions, the same acute cases and the same cases with nodules in the skull, skin, etc.

Death results in the same way and almost as certainly although the author is not prepared to admit that cure is impossible or has never occurred.

It is, however, a chronic disease as a rule while lymphæmia is commonly acute. These points will be more apparent subsequently.

Etiology.—There are undoubted congenital cases of myelæmia associated with sclerosis of the bones. These are to be considered a maldevelopment rather than overdevelopment. That they should occur is not very surprising since the tendency for the marrow to revert to a primitive type in myelæmia is well established and a persistence of the primitive type to the exclusion of adult specialisation would be a type of maldevelopment to be looked for in the marrow as in other tissues.

Hereditary transmission and passage of the infection from person to person have been recorded but on examination the records are found to be far from convincing.

Age and Sex.—On the whole those of the male sex are more frequently attacked than females as was noted to be the case in lymphæmia. The disease is quite uncommon in children which affords a contrast with lymphæmia but it is certain that some cases reported as acute examples of the latter disease were in fact acute myelæmia. The acuter form of either disease is more common among the children attacked.

Onset.—This is characteristically vague and often unrecognised by the patient. The symptoms for which treatment may be asked are many, anæmia, headache, loss of strength, etc.

In a certain proportion of cases advice is sought on account of swelling of the stomach and this is found to be due to an enlarged spleen. In some also gastric symptoms referable to the same enlargement are the first obvious signs.

A primary symptom not met with in lymphæmia so far as the author is aware is acute Menière's disease, *i.e.*, sudden deafness with tinnitus and apoplectiform symptoms.

General Symptomatology.—In myelæmia we are dealing with a characteristically chronic disease whereas in lymphæmia it was mostly acute symptoms that had to be described. The other great difference between the two resides in the presence of a very large spleen in one and of swelling of lymph glands in the other. It is true that either of these may occur in either disease, but lymphadenoma in myelæmia or splenomegaly of the massive type in lymphæmia are alike exceptional.

The difference that this will make in the general symptomatology is easily understood. The symptoms referable to the different systems are dealt with separately below but where a system seems to have escaped full mention it is to be understood that the description of that system given under lymphæmia applies.

Fever.—The description of the variations of temperature in lymphæmia applies in myelæmia also (see page 55).

Nervous System.—In the main the symptoms are those of lymphæmia but we have also to note the occurrence in myelæmia of the combined sclerosis met with in Addisonian anæmia (see page 239). This is very rare although *formes frustes* of the same probably occur much more commonly than is generally recognised.

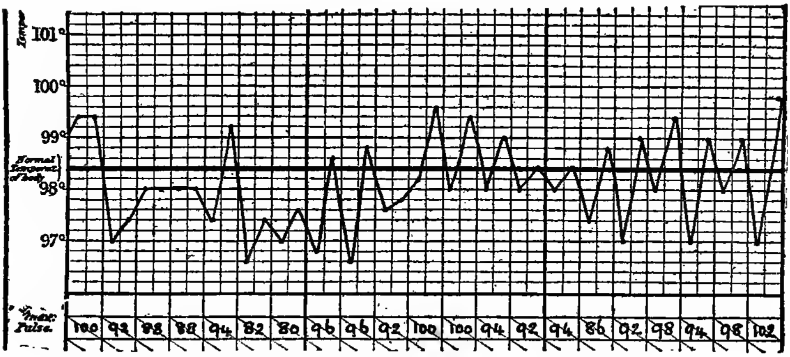


FIG. 18.—Three weeks' temperature chart from a case of myelæmia in a man aged thirty-eight. Showing slight irregularity only.

Tenderness of the bones on percussion is more frequent than in lymphæmia.

Pain in the stomach and even acute crises of pain comparable in severity to those of tabetic crises are sometimes met with when the spleen is enlarged and the capsule inflamed. They are further dealt with on page 98.

Special Senses.—In a few cases persistent tinnitus has been the first sign of myelæmia. Such cases have been rather fully studied, more especially those in which the onset of tinnitus has been very acute and temporarily disabling, *i.e.*, the classical Menière's symptoms. It is strange that the majority of the examinations which have been made of the inner ear in order to elucidate the causes of tinnitus have been carried out in cases of leukæmia. The usual finding, as one would expect from the suddenness of the onset of symptoms, has been hæmorrhage into the delicate structures of the cochlea, etc. It would appear that this is usually predisposed to by leukæmic infiltration beneath the endosteum in this situation but it will be understood that the space available prevents this attaining any great development.

The tinnitus is usually accompanied by deafness which may also occur as an accompaniment of hæmorrhages into other parts of the auditory system but deafness without tinnitus is not common as a result of myelæmia. When it does occur it is usually of slow onset and depends on leucocythæmic infiltration of the inner ear or of structures in a position to interfere with some part of the auditory apparatus.

The prognosis is bad as there is small probability of the hæmorrhages being absorbed and even less of the infiltrations disappearing. Both may occur but are very rare.

Changes in the eyes are less common than they are in lymphæmia corresponding with the increased frequency of the acute form in the latter disease. Hæmorrhages into the retina are met with and also leukæmic retinitis. Among the great rarities are nodular growths on the conjunctivæ.

Marrow.—In its general and naked eye features this is similar to that of lymphæmia. It is hypertrophied, *i.e.*, the cell-forming marrow encroaches on the fatty part and in many bones completely displaces the latter. It shows similar variations in colour.

Microscopically it shows a great predominance of cells similar to those found in the blood or of their mother cells, the myelocytes and pre-myelocytes.

The red-cell-forming tissue, which is at a minimum in lymphæmia, may be very well represented by foci of nucleated red cells irregularly disposed and these show variations in size, shape and staining reaction to an extent paralleled by that of similar changes in the blood stream. As one would expect the changes in the marrow commonly appear more advanced than those in the blood although of the same nature. This is because the more adult cells, the most highly specialised, are those which reach the blood stream in the largest numbers and are in consequence less numerous in the marrow.

If it be desired to study the changes in the marrow, as is especially likely to be the case when the blood changes have not been marked, it is well to make smears from the fresh tissue obtained post mortem.

The author's method of doing this is to cut out a triangular wedge from the vertebræ with the aid of a saw and to press one side of this on to a clean slide. No lateral or sliding movement is to be allowed as this causes distortion of the cells and destruction of their relations to each other. The slide is then treated just as if it were a blood film that was to be dealt with. The marrow should never be moistened or allowed to come into contact with water before the film is made. A piece of the sternum removed with a trephine can be used but is not so satisfactory. Rib marrow is almost useless for this purpose.

Blood.—The red cells may be very nearly normal in number for a long while but eventually become diminished. They seldom fall below one million per c.m.m.

As the severity of the anæmia increases the type of red cell becomes more and more irregular. Even when there is little or no diminution in total number there are to be found (apart from the nucleated cells) cells in which the staining is polychromatic or which exhibit strippling or are too large or too small. Poikilocytosis is also met with.

Later the type of red cell change associated with Addisonian or "pernicious" anæmia is commonly met with.

Nucleated red cells are almost invariably present in considerable numbers owing to the fact that the stimulus which produces the disease has incidence on white- and red-cell-forming marrow tissues alike. The author has met with one case in which nucleated red cells were entirely absent.

All varieties of nucleated red cell are met with. The nucleus is very variable and transition forms between normoblasts and megaloblasts are very frequent. Most of the cells stain abnormally and in a few there may be no trace of hæmoglobin. Such cells are of course very hard to identify. About 10 per cent. commonly show signs of division and actual mitotic figures are usually to be found after a little search in a typical film.

The white cells are as a rule more numerous than is the case in lymphæmia and commonly exceed 500,000 per c.m.m. More than 1,000,000 per c.m.m. have been recorded but such extreme counts as this are not often encountered. The number of red and white cells may be equal in the late stages of the disease. This also is uncommon. On the other hand the white cells may fall to a very low figure, *e.g.*, below the normal and even below 1000 per c.m.m. This is usually a terminal phenomenon and is very rare but in other cases when the condition of the patient is improving it is no uncommon matter for the normal numbers to be reached. There are very rarely stages in which no alteration in the blood can be made out beyond the anæmia. The author has met with one case in which the patient was obviously seriously ill but the number of white cells was only 6000 per c.m.m. and the myelocytes were only 2 per cent. A few of those present showed mitosis.

Of the white cells a majority are myelocytes and these cells are bigger than ordinary leucocytes and are mononuclear. The nucleus is usually to one side and is not uncommonly indented. It stains rather poorly, certainly less deeply than that of the leucocytes. The granules differ in different cells and are in very few apparently of more than one sort. They are similar to those of their descendants and are thus neutrophil or eosinophil or basophil. These cells are accordingly called neutrophil, eosinophil and basophil or mast cell myelocytes.

The corresponding leucocytes are also increased in number and an increase of mast cells is especially characteristic as this does not occur in any other disease to anything like the same extent. Under treatment the mast cell is usually the first to disappear from the blood stream.

The predecessors of the myelocytes are met with and in the rare acute cases may predominate. They are cells with a darkly staining rim of protoplasm and often show nucleoli.

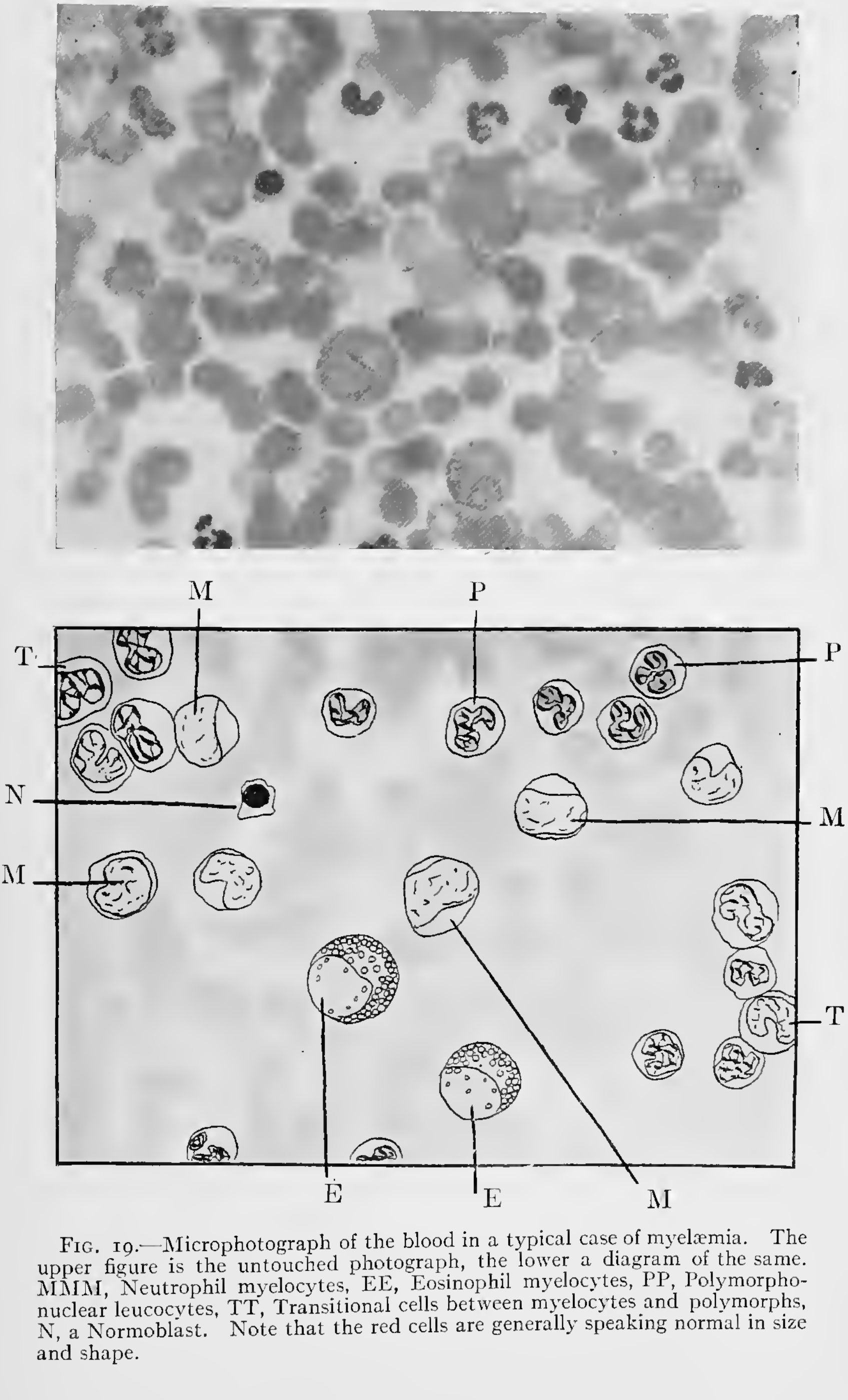


Fig. 19.—Microphotograph of the blood in a typical case of myelæmia. The upper figure is the untouched photograph, the lower a diagram of the same. MMM, Neutrophil myelocytes, EE, Eosinophil myelocytes, PP, Polymorphonuclear leucocytes, TT, Transitional cells between myelocytes and polymorphs, N, a Normoblast. Note that the red cells are generally speaking normal in size and shape.

Their exact form varies considerably and it is usually safe to say that any cell not obviously normal in the blood stream nor a myelocyte is probably a pre-myelocyte.

Fragments broken off from cells, cells with more than one nucleus, cells of such size as to deserve the appellation of giant cells and other atypical forms may be met with.

Cells indistinguishable from the small mononuclear or lymphocyte of normal blood are usually increased in number but are in a diminished percentage of the cells present as against the percentage found in health.

The type of cell found in the blood changes from time to time and a change of type to that found in lymphæmia is spoken of by some authors. This is nothing but a reversion to a more primitive type and is in no sense a change from one disease to the other. It has been already explained (page 49 et seq) that this reversion also occurs in lymphæmia and that if it progresses far enough the blood changes in either disease may almost exactly resemble that met with in the other—supposing both to have reverted.

Platelets are usually increased.

The Spleen.—The enlargement of this organ in a typical case is best described as massive. It may reach to the pelvis and as much as two or three inches across the middle line. All stages from this to an enlargement that is only just palpable are met with but do not necessarily point to similar variations in the blood. It is true that in a case improving spontaneously or under treatment the numbers of circulating white cells and the size of the spleen as a rule run parallel but in some cases the blood becomes normal without any diminution in the splenomegaly.

Sometimes the enlargement is observed by the patient and causes him to seek medical advice, in more cases it is first discovered by the physician and, in even more perhaps, the first symptom is in reality referable to its overgrowth but not at first sight connected with it.

Continuous pain is often complained of and also pain after food, when it may be presumed that free motility and expansion of the stomach are interfered with by the presence in the abdomen of a large tumour. A dull pain not well localised and described as of a dragging nature is also complained of in some cases.

If there is peri-splenitis and adhesions have formed between the spleen and neighbouring structures such as the diaphragm pain is likely to be a more prominent feature and to it may be added breathlessness and lesions of the respiratory system on the left side.

Acute attacks of pain in connection with the spleen are usually due to acute peri-splenitis. This may be very sudden in its onset and accompanied by vomiting, pyrexia and abdominal tenderness. There are in fact all the signs of an "acute abdomen" and operation may be undertaken on the supposition that there is some acute surgical emergency to be dealt with. These attacks usually subside after a short time leaving adhesions which may give rise to further trouble or only thickening of the capsule which is comparatively innocuous by itself. Fomentations and rest in bed comprise the chief points in treatment.

Rupture of the spleen is rare and so is torsion but it will be readily understood that the increased weight of that organ may cause elongation of its pedicle and thus predispose to twisting.

Post mortem the spleen is usually firm and, on section red or greyish in colour. It may be greenish. The cut surface is commonly homogeneous and bleeds little in a chronic case. The Malpighian corpuscles sometimes stand out but not very commonly. Rarely there are definite areas of a whitish colour or at least of a different shade to that of their surroundings which stand out both beneath the capsule and in the substance of the viscus. These are due to lymphoid nodules which have undergone a myeloid metaplasia and are then virtually marrow tissue although not situated in the bones. In a few cases there has been amyloid degeneration; areas of softening and infarcts may be met with.

Similar changes affect any accessory spleen that may be present.

Splenectomy has been carried out in between twenty and thirty cases and will be subsequently referred to (page 107).

Lymphatic Glands.—These are not as a rule so affected as to

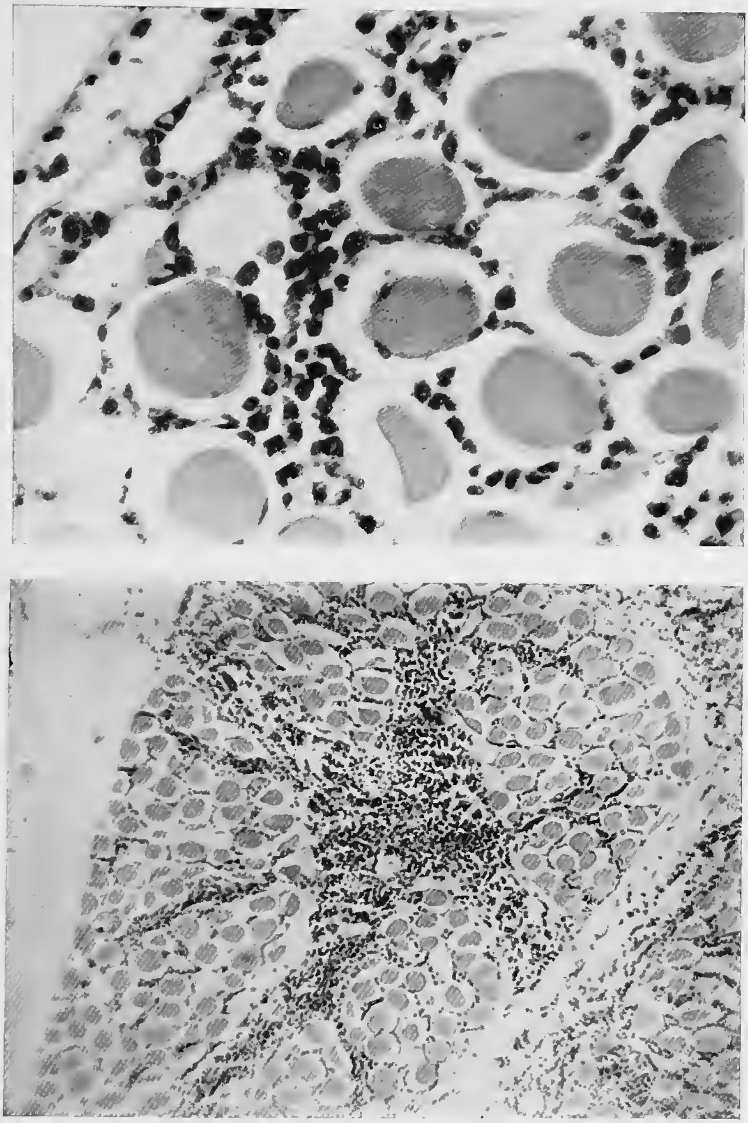


Fig. 20.—Section of muscle from a case of acute myelæmia. It will be noted that the muscle fibres are not destroyed but separated by growth of myeloid tissue between them. This originates in the primitive cells of the connective tissue supporting the muscle fibres.

give rise to clinical signs of enlargement but careful examination will often disclose some slight degree of hypertrophy. Glandular enlargement is usually found to be present after death in situations inaccessible to examination during life.

Microscopically they are found to be forming cells similar to those met with in the blood and to present a structure like that of the marrow, except that red-cell formation in the glands is apparently not met with.

They may show all the gradations of colour from red to greyish green or even bright green but are more usually of a yellowish tint on section.

The hæmolymph glands are frequently in a state of increased activity.

Muscular System.—There may be infiltration of muscles. (See Fig. 20.)

Osseous System.—Periosteal nodules are not nearly so often met with as in lymphæmia, have, in fact, been reported in a very few cases and all these of the acute variety. They are similar in distribution to those of the latter disease.

Tenderness on percussion of the bones is a frequent sign of hyperactivity of the bone marrow in this as in other disorders. Absorption of the trabeculæ within the bone is also a common finding and may be detected by the X-rays.

Spontaneous fractures are not met with.

Respiratory System.—In the main the clinical signs referable to this system are the same as those met with in lymphæmia. There is often dyspnœa and this may be more than the degree of anæmia would account for—this sort of dyspnœa is sometimes referred to as toxic in origin. There is another possible but very rare cause of it, viz., leukæmic infiltration of the submucous tissues of the bronchi. So far as the author is aware this has only been recorded in one case but the toxic dyspnœa is quite commonly encountered.

Leukæmic nodules in the lungs other than submucous infiltrations are not common and do not as a rule give rise to any definite physical signs or symptoms.

The respiratory system may be affected secondarily to enlargement of the spleen and less often to enlargement of the liver.

It is obvious that either of these organs will press on the space normally occupied by the bases of the lungs and will therefore hinder their expansion.

It thus happens that a patient may come to his medical man complaining of dyspnœa and on examination exhibit a dull area at one or other base. This may not be accompanied by much downward enlargement of the spleen or liver and even if this be present it may easily be missed if a somewhat hurried examination is necessitated by the circumstances, *e.g.*, many patients to be examined in a short time.

The physician will find dullness at the base of one lung and absence of breath sounds. There will also be dyspnœa and perhaps some elevation of temperature. The patient may also be obviously anæmic and give a fairly long history of increasing respiratory embarrassment.

It will not be very surprising if the physician suspects hydrothorax and he may put in a needle to see whether his diagnosis of fluid is correct or not.

In this way a needle has unwittingly been pushed into the liver and into the spleen in different cases of myelæmia.

But apart from the simulation of fluid in the chest there are other results in compression of the bases of the lungs. There is an actual tendency to the development of pleurisy with effusion and this, as would be expected, is more commonly associated with attacks of peri-splenitis than with any disorder of the liver.

The effects of pressure on the lung—through the intermediary of a fixed or nearly fixed diaphragm—are also seen in the shape of œdema and collapse with a particular liability to all the disorders that lungs are prone to.

The fluid drawn off in an attack of pleurisy is similar to that seen in non-tuberculous conditions and very rarely contains cells similar to those in the blood unless it is an actual hæmorrhagic effusion.

Chylous fluid has also been reported and does not differ from that found in other situations, which is subsequently referred to (page 102).

It may also be mentioned here that the pericardium may be affected by acute inflammation in the same way that the pleura is. It also may contain chylous fluid.

When nodular growths are present on the back of the sternum, which is a rather favourite site in those few cases in which nodules are present at all, there may be various interferences with the lungs and heart but these are not as a rule very serious as these nodules are usually not of great size in this position. Involvement of the pleura in nodular growth is also possible but not common and this again is also of the pericardium.

Alimentary System.—This also has been to a large extent dealt with when describing lymphæmia and the symptoms of enlarged spleen which involve the alimentary system, such as vomiting and indigestion, have also been noted.

There are, however, a few additional facts to be considered. A bad state of the mouth is not nearly so often noted as in lymphæmia and usually only in terminal phases of the disease. In the same way any sort of nodular affection of the intestinal tract is uncommon.

This is perhaps a convenient place to refer to the ascites met with in myelæmia and very rarely in lymphæmia.

Ascites may be due to the anæmia and accompanied by œdema of the extremities and all the signs of a failing heart. In this case it is seldom extensive but is almost always a terminal and a grave symptom.

In other cases it may depend on pressure on the veins such as may be exerted by enlarged glands or on changes within the liver of a fibrotic nature. These will be presently discussed. In such cases the ascites may be a symptom which necessitates frequent tapping of the abdomen. The fluid withdrawn is usually clear and contains few cells, rarely there is a considerable cell content and the cells may be similar to those met with in the blood. It may be remembered that hæmorrhage into the peritoneal cavity—apparently from the rupture of mesenteric or omental veins—is among the rare happenings of leukæmia as is also infiltration of the omentum. Either of these may give rise to considerable difficulty in diagnosis and will produce a dullness hard to explain except on the hypothesis of the presence of ascites.

In a few cases there has been chylous ascites and the exact pathology of this is not determined. The fluid is milky or at least opaque and contains very fine drops of a substance of which the nature is in doubt. These form an emulsion which is more perfect and composed of finer particles than is milk. Under the microscope the globules may appear only as specks of light. This is a rare complication and the treatment is the same as for any other variety of ascites.

Hæmorrhages from the intestinal tract or stomach, constipation and, in particular, diarrhœa are symptoms which may be met with. The latter is apt to be intractable if the strongest drugs are not used. Pulv. Kino. Co in doses of gr. v every four hours is often useful. In the majority of cases there are some symptoms referable to the alimentary system but these are not often of an urgent nature.

Liver.—This is not infrequently very much enlarged and is seldom normal in size. The enlargement is in part due to congestion and in part to the presence of myeloid tissue along the vessels and in Glisson's capsule. The origin of this is similar to that of tumours, etc., and has been discussed on page 49 et seq.

The enlargement may give rise to some variety of symptoms of which ascites has already been mentioned above. Jaundice may depend on pressure on the bile ducts which, of course, run in Glisson's capsule and are there particularly exposed to pressure by the newly arisen myeloid tissue. Less commonly it may depend on the presence of enlarged glands in the portal fissure. The gall bladder is usually normal. Gall stones are rare.

Pain may also be due to liver enlargement and may be of a dull aching character or acute and due to perihepatitis. The latter, however, is not common clinically although a little thickening of the capsule is a fairly frequent post mortem finding.

Respiration is also hampered by enlargement of the liver (see page 99).

Toward the end of the disease the liver is usually fatty and at a post mortem examination often appears pale and feels greasy. In one or two cases it has been seen during life and

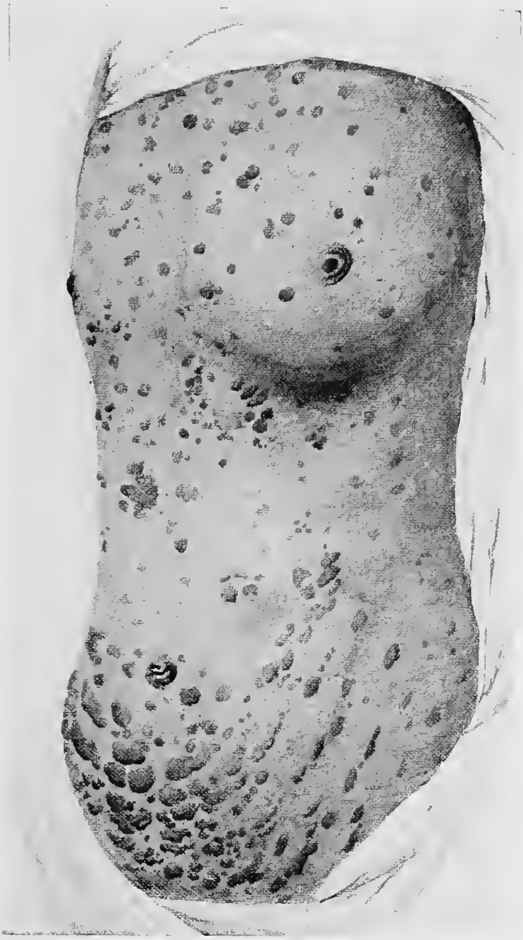


FIG. 21.—Photograph of a water colour drawing of skin nodules in a case of myelæmia. (By kind permission of Drs. H. D. Rolleston and Wilfrid Fox.)

has been reported as red and shiny. These were cases in which laparotomy had been performed before the diagnosis was arrived at.

Urogenital System.—The description given under Lymphæmia (see page 75) applies also in myelæmia but, corresponding to the larger number of chronic cases in the latter, there are fewer of the acute signs and symptoms of disease.

The Skin.—Here again the description given under lymphæmia applies. All sorts of lesions from simple erythema to nodule formation are met with. In one case the author noted a very chronic ulcer on the dorsum of the foot. This had been caused by trauma and only healed very slowly even when the patient was kept in bed. It had remained stationary while the patient was up and about, as he was before his medical man told him that he had a tumour in his abdomen and sent him to hospital for treatment.

Glands—Other than Lymphatic.—The symmetrical glandular syndrome has been met with but is very rare. Otherwise there is little to record (see also page 79).

Course.—As has already been pointed out this is usually chronic from the outset. The acute cases are not distinguishable clinically from acute lymphæmia and there has no doubt been considerable confusion between them in the past.

Death takes place from exhaustion consequent on severe anæmia in some cases and from complications in others. Of the latter hæmorrhage into the brain is not very rare and rupture of the spleen has been recorded. A few cases have died in asylums.

It is practically impossible to give a prognosis, just as we noted was the case in chronic lymphæmia, and one can only say that the disease is almost certain to terminate in the death of the patient but that there may be many useful years of life in front of him before this occurs. As a rule one can promise at least one total remission of symptoms if X-ray treatment can be carried out thoroughly. This, unfortunately, is by no means always the case.

Remissions are very common, almost the rule, in this disease. By a remission is meant a return to the normal of the blood and the general health of the patient. This is seldom absolute, *i.e.*, there may still be slight abnormalities in the blood, the patient may feel very much better but not think he is as well as he was before the disease became established or there may remain a large spleen or liver although the progress otherwise deserves to be called a remission. Such varieties of remission will be considered true remissions for the purposes of the following remarks.

They may occur (1) spontaneously (2) as the result of treatment—usually arsenic or X-rays and (3) owing to some intercurrent disease.

Spontaneous remissions are hard to be sure about as the patient is no doubt being treated in some way if there is an opportunity to observe a remission and to this method of treatment any improvement that he may show is likely to be ascribed. It seems certain, however, that the disease does undergo spontaneous remissions similar to those met with in lymphæmia, in Addisonian anæmia and in other diseases.

Treatment with arsenic is most likely to be responsible for a remission which can probably be ascribed to successful therapeutics but as X-ray treatment becomes more frequently applied this will claim a larger number of successes. Bone marrow has also been said to exercise a good effect in some cases and so also have benzene and other drugs. Some of these may be genuine therapeutical remissions but it is quite probable that some are spontaneous remissions happening to occur when the patient is under treatment.

Intercurrent disease does not as a rule affect the course of myelæmia unless it be of a septic nature, *e.g.*, erysipelas or abscess formation. In this case there may be a quick fall in the number of circulating white cells and the blood picture changes to the ordinary polymorph leucocytosis of such infections. As the septic process dies out there may be a return to the blood of the abnormal cells or the normal blood picture may appear and the patient at the same time improve in health.

In other cases the septic infection although coinciding with the improvement of the leukæmic process may prove fatal to the patient. In certain such cases the morbid histology may be very confusing as the characteristic liver changes are masked by the presence of septic signs and also because the abnormal cells met with in Glisson's capsule may be actually necrotic and not recognisable.

The results of sepsis in modifying the disease process are seen especially in lymphæmia because the acute nature of the disease and the stomatitis favour the onset of sepsis (see also page 71).

It is obvious that we have in this modification of the disease under the influence of septic processes an interesting parallel with the similar modification that may occur in cancer. It has been already pointed out that the author does not believe that leukæmia can be properly regarded as cancer of the bone marrow or of other blood-forming organs but it is undeniable that there are analogies between the two (see also page 90). The most interesting in some ways is that now under discussion. Not only may cancer disappear or be modified by X-rays and septic processes but it may also necrose and vanish when Coley's fluid is used. This contains the toxins of the streptococcus erysipelatis and the bacillus prodigiosus. In leukæmia we find X-rays similarly useful and the same remissions after a septic invasion. Coley's fluid has only been used in one case of leukæmia so far as the writer is aware and was of small value. This case, however, did not undergo a regular course of treatment.

It would seem very legitimate to employ it in chronic cases.

Clinical Varieties.—These are the acute, the chronic and those associated with the various syndromes mentioned on page 82.

Complications.—Intercurrent disease is not very commonly observed but several cases of tuberculosis complicating leukæmia have been observed and a few isolated cases of other diseases. Among the latter are the septic processes already referred to and epilepsy, syphilis, typhoid fever, lobar pneumonia, various skin diseases, heart disease, etc.

There does not seem any tendency on the part of these to modify the course of the leukæmia, except as mentioned above when dealing with remissions.

Diagnosis.—Many, indeed most, of the remarks made on page 84 when speaking of lymphæmia apply equally well here. This is particularly true of the rarer forms in which there are skin or skull nodules or in which the onset is so acute that the clinical picture is dominated by some such symptom as severe stomatitis which does not at first sight suggest a disease of the blood-forming organs as its underlying cause.

Of course in the great majority of cases there will be marked or at least easily recognisable splenomegaly when the patient first comes under notice and this will suggest a blood examination which will, in turn, provide a certain diagnosis.

It is therefore necessary to confine one's remarks under the heading of diagnosis very largely to the class of case which is rare—very rare in individual experience—although this may seem to result in laying stress on the out of the way aspects of disease.

In some cases even when the blood has been examined there may be serious difficulties in the way of correct and confident interpretation of the results. This is especially the case when the blood contains largely mononuclear cells of a primitive type. In this eventuality it may be actually impossible to say with which variety of leukæmia we are dealing. It should be noted that the presence of a few myelocytes is common in all stages of lymphæmia so that their presence in a case is not diagnostic of myelæmia. On the other hand eosinophil myelocytes and mast cell myelocytes are not found in lymphæmia so that the presence of these is almost diagnostic of myelæmia. The number and variety of nucleated red cells may also be of assistance since there are usually more in myelæmia and what there are are more likely to include megaloblasts.

When there are no blood changes or these cannot be ascertained the diagnosis between the two varieties can be made with a good deal of assurance from a consideration of the physical signs.

The differential diagnosis between the two varieties of leukæmia has fortunately very little importance from the point of view of treatment which is the same in each.

The diagnosis from splenic anæmia and even from cholæmia if the blood condition is not pathognomonic may present some difficulty but this is seldom likely to be the case now that these diseases are more known than was formerly the case. The points in the differential diagnosis are mentioned on pages 145 and 232.

From Hodgkin's disease the blood findings usually at once differentiate leukæmia (see also page 128).

From Addisonian anæmia the diagnosis may occasionally be difficult. This is due to the fact that in that disease a few myelocytes are commonly found in the blood toward the end. The red cells may show identical changes in the two diseases. An actual increase of white cells—apart from changes incidental to intercurrent infection—rules out Addisonian anæmia.

Treatment.—This in general follows the same lines as in lymphæmia and X-rays and arsenic are the favoured and most satisfactory therapeutic agents. It has been customary to apply the rays to the spleen but this is not without some disadvantages as the functions of that organ are multiple and there is danger of disturbing others than those aimed at. The same objection holds much less if at all in the case of the marrow and in consequence it is better to ray the long bones. The results seem to be the same in either case. The whole matter is more fully dealt with on page 345 and the subsequent pages.

Splenectomy has been several times performed and has never proved fatal from any modification that it produced in the leukæmic process. It has, however, never been successful owing to what may be called the surgical risks of the operation and all the cases have died from shock, hæmorrhage or sepsis. It is true that one case reported is said to have recovered but there is grave doubt whether this was a case of leukæmia at all. It is usually said, in view of the foregoing facts, that splenectomy is unjustifiable. It seems to the author that they do not bear that interpretation when it is borne in mind that these operations were performed before the technique of splenectomy was as satisfactory as it is at present and especially before the treatment of surgical shock was on a sound basis.

It would appear that the operation of splenectomy for leukæmia has, in the present state of our knowledge, precisely the same justification that belongs to any other operation of an experimental nature for the cure of an otherwise incurable disease. It should, however, first be tried on animals; this may indeed have been done but the author is not aware of the results if this is the case. No operation would of course be undertaken until a remission had first been procured by the use of X-rays. When the anæmia is severe the friability of the tissues and the tendency to hæmorrhage are so marked that no surgeon would be likely to undertake a major operation. Of recent years the time-honoured methods of treating leukæmia have been reinforced by certain additions to our therapeutic weapons.

Selling of Baltimore noted that certain workers in a benzol factory suffered from a severe aplastic anæmia due to chronic intoxication with poisonous fumes. His paper was widely read and it was thought possible that this effect of benzol in depressing the activity of the blood-forming organs might be turned to account in leukæmia. Many physicians have now tried it but the cases in which it has given good results have not yet been long enough under observation so that the likelihood of cure cannot be stated.

So far as is known benzol acts very similarly to arsenic or the X-rays, *i.e.*, it produces immediate and marked improvement in some cases and very little effect in others. Of those improved some have already relapsed and benzol has failed of the maximum effect on the second occasion of its employment. In addition it does undoubtedly produce untoward symptoms in a small minority. These were probably persons of unusual susceptibility to the drug. Among the symptoms of poisoning are vertigo, hiccough and inflammation of mucous membranes, *e.g.*, bronchitis. There may also be unpleasant gastric symptoms. Any of these should suggest a smaller dose or even that administration of the drug be discontinued.

By most people benzol in doses of 3 grammes is tolerated without difficulty and may be used continuously for many weeks. The dose is to be given every day.

A convenient method is to give sixty drops each of benzol and olive oil in a capsule. This obviates unpleasant taste in the mouth and the oil seems to ward off gastric discomfort.

Thorium and meso-thorium are allied to radium and are cheaper but rather less active. They have been used both by external application over the spleen, by internal and subcutaneous administration. They have been fairly widely used but the results are conflicting and, considering the difficulty of dosage, etc., it may be said that they offer no special advantage.

Radium has been applied over the spleen with success but, as already noted, applications to the spleen are not very advisable. It might be applied over the sternum—a situation involving also action on the vertebræ which is an advantage.

Salvarsan has been used as a means of administering arsenic. As it is a benzol derivative one might, theoretically, claim a double advantage. Actually there can be no doubt that salvarsan is an uncomfortably powerful drug except in the hands of an expert. It may be employed where it is desired to get the patient quickly under the influence of arsenic.

Of these more recent therapeutic efforts none is certainly superior to arsenic and the X-rays but they are of value as alternative methods. It is well known that arsenic loses its power over the disease after a while and the same is true of X-rays. But X-rays will sometimes produce a good result when arsenic is no longer of use. In the same way benzol may be of value when X-rays have failed. It is even said that it acts more promptly when X-rays have previously been employed.

Radium again has proved successful when other means have had to be discarded.

Hence the value of these newer methods consists in their use in series especially when arsenic or the X-rays have failed.

For the rest the treatment of myelæmia must be purely symptomatic, in which connection no drug calls for especial mention nor is any special dietary indicated.

CHAPTER VI

HODGKIN'S DISEASE AND GAUCHER SPLENOMEGALY

HODGKIN'S DISEASE

Synonyms.—Lymphadenoma, pseudo-leukæmia, adenie, etc.

Nature.—This disease on the one hand approaches the avowedly infective processes, especially tuberculosis, and on the other the leukæmias. To the latter it is allied as a generalised affection of the blood-forming organs, to the former in view of certain histological features, the accompanying pyrexia, the frequent spread from one set of glands to those most nearly related anatomically and the often noted antecedent history of throat trouble; the latter being of especial interest in view of the usual commencement of the obvious disease in the cervical glands.

The author inclines to the view that the disease will eventually be proved to be infective in nature but not necessarily that the infective agent will be found in the glands themselves.

General Pathology.—This disease is a distinct pathological entity and it is not the same as nor does it tend to pass into the various other disorders which some authors delight to group together under the comprehensive titles of Lymphadenoma and Pseudo-leukæmia.

We do not know what initiates the train of symptoms to which we give the name Hodgkin's disease but we do know the order in which these symptoms are likely to develop, the clinical types of the disease and the histological basis on which it rests.

It is commonly said to be a disease of lymphatic glands and on this slight mistake has been erected a structure which might well have hidden even a less obscure pathology. It is—like leukæmia—a disease of lymphoid tissue wherever placed and it has the power of calling into being lymphoid tissue in any area or organ developed from the mesoblast of the embryo.

Like leukæmia, it may be acute or chronic and terminates in severe anæmia. The nature of the process is similar in the two diseases.

Clinically the disease is often first manifested in the cervical lymphatic glands although there are a considerable number of cases in which some other group was first involved.

There is often a history of sepsis in structures, such as those of the mouth and throat, in anatomical relation with these glands.

In any case the glands slowly enlarge and after a while some adjacent group also becomes obviously affected. From this all the other glands of the body may be affected in order—as far as the clinical appearances go. The author does not wish to be understood as saying that the infection is actually conveyed from gland to gland. The spleen also enlarges and the liver may be affected. There may also appear lymphoid nodules in the skin and in other structures similar to those affected in the nodular varieties of leukæmia.

At some time in the course of the disease and not as a rule at the commencement there develops anæmia of varying degree —later this becomes very severe and if the patient does not succumb to tuberculosis may be the principal cause of death.

In the course of the disease there may be remissions of varying degree and the previous good health of the patient may be to all appearances completely re-established. In some cases the whole course of the disease is very rapid and death may result in a few months or less from the onset, in others the disease is extremely chronic.

The changes found in the affected tissues are found to vary considerably according to the stage of the disease, in the early stage there is great cellular activity and in the later much fibrosis so that the cellular changes are seen at a minimum. A similar process has already been described as occurring in the blood in leukæmia and has there given rise to the myth of change in type from myelæmia to lymphæmia. In the same way a change of type from cellular to fibrotic Hodgkin's disease might be said to occur—but unfortunately no one has seen fit to do so.

The above is the usual process or pathology of the disease; the histological changes and the morbid anatomy are dealt with later in their appropriate places.

Etiology.—This is still unknown but very many suggestions have been made—which perhaps constitutes good reason for concluding that none of them are correct. The coincidence of septic processes in the neighbourhood of the first glands to enlarge is certainly interesting but does not take us very much further in our search for an etiological basis. Septic changes in the mouth are rather the rule than the exception and unless we suppose that there has, in these cases, been some special germ introduced into the body we can hardly explain the characteristic changes in the glands. If there is a special microorganism it must be noted that the changes at its presumed site of invasion are in no way characteristic, for all sorts of septic processes have been reported. This is of course no proof that a special organism does not exist but it shows the difficulty in accepting the preceding sore throats, etc., as etiological factors.

There have also been described several organisms in the glands including spirochetes. Of these the tubercle bacillus has been most frequently encountered but has always been accompanied by the histological lesions characteristic of its invasion. Some have supposed that Hodgkin's disease is a special form of tuberculosis but there is ample evidence to show that the latter is a frequent terminal infection so that it seems useless to invoke its assistance to explain the whole process. Again in many cases it is not found nor does animal inoculation from these cases produce tuberculosis.

Hereditary and familial cases have been reported but never with such frequency as to allow any weight to be given to the hereditary factor as an etiological feature.

The male sex is certainly most often affected but this is what we have come to expect of the generalised affections of lymphoid tissue and is inexplicable if interesting.

Age and Sex.—The confusion which has for a long time existed as to exactly what constitutes Hodgkin's disease has made the determination of the age and sex incidence somewhat difficult. It is certainly the fact that males are more often affected than females, but in what proportion one cannot say. It is probably quite as much as 2 to 1 as is the case in lymphæmia.

Children are certainly very frequently affected but after the age of fifteen to seventeen the disease would seem to become less common until the age of 25 to 45 is reached. In the first part of the latter period the disease is fairly common, in the second less common. Cases in which the first signs appear in old age are rare but, even so, probably more often noted than is the case in lymphæmia.

Onset.—The onset is very variable. In the majority of cases there is first noticed some glandular enlargement in the cervical region. This is either unilateral or at least very much more marked on one side.

Associated with the enlargement there may be dyspnœa or other pressure symptoms and these latter may be the immediate cause of the patient's seeking medical advice.

When, on the other hand, the mediastinal or abdominal glands are first affected the patient may complain of almost any symptom referable to those regions.

An interesting but not particularly common mode of onset is first manifested by fever and general malaise. This may occur without any obvious glandular swelling and may be found to be but one phase of the recurrent fever mentioned on page 126.

An acute onset with general enlargement of many groups of glands in various parts of the body undoubtedly occurs but is rare. Clinically it closely resembles tuberculosis generalised throughout the lymphatic glands.

General Symptomatology.—This includes the effects of pressure by the enlarged glands on the one hand and on the other the usual symptoms of severe anæmia. The latter may be delayed for a long time.

Exceptionally there are signs and symptoms due to nodules of lymphoid growth in various of the internal organs. These are likely to resemble those already mentioned when speaking of the analogous growths in leukæmia and will not be specially referred to in the following paragraphs except in a few instances.

The general symptomatology is, in brief, progressive enlargement of glands and progressive anæmia.

Nervous System.—The symptoms which affect the nervous system are almost entirely those of pressure. The fibrous lesions of Hodgkin's disease seem to produce pressure symptoms far more readily than the lesions of other glandular affections.

Pain in the arm is a common sequence to enlargement of cervical or axillary glands. The actual tumours are not themselves painful in the majority of cases but are commonly so in the acute cases and may be in others.

The author has seen one case in which there was a condition which clinically resembled meningitis and which was found post mortem to have considerable œdema of the membranes of the brain.

There is at least one case reported in which the histological changes were certainly those of Hodgkin's disease as here defined and in which there were nodules on the dura mater. These were three in number but there is no mention of symptoms in connection with them. That symptoms might arise in such cases is obvious.

Special Senses.—There is nothing of note to record.

Circulatory System.—The heart in the later stages may be markedly affected by fatty changes and may then become incompetent. Beyond this there is no change commonly met with in the circulatory system except such as may be produced by the enlargement of glands in a purely physical manner. Thus there may be and often is compression of the vessels in the thorax and this may give rise to cyanosis with œdema and swelling of the neck. Similar changes may occur in the extremities or the abdomen. As there is often a large mass in the mediastinum some displacement of the heart and large vessels is not at all uncommon.

Purpura and bleeding from the mucous membranes are not common but are fairly frequent in the acute cases. They are usually terminal symptoms.

Peri-arterial fibrosis is one of the most characteristic changes in the glands but is not met with in other parts of the body.

Marrow.—This is commonly increased in extent and if there has been interference with the proper oxygenation of the lungs during life there will probably be an increase of red-cell formation directly due to this.

Marrow examinations have not very often been made but there would seem to be as a rule a distinct increase in the eosinophils.

The proportion of leucocytes and lymphocytes is variable and probably depends to a large extent on the stage of the disease and the degree of associated anæmia.

The typical changes of Hodgkin's disease such as are met with in the glands are also to be found in the marrow, as a rule in scattered foci and not evenly disseminated throughout the tissue. At the post mortem examination these may be seen as white areas.

If there is severe anæmia the red cells in the marrow will show changes similar to those found in the blood, *i.e.*, polychromasia, etc.

Blood.—It may be at once said that there are no characteristic or pathognomonic changes.

The red cells are often normal when the patient is first seen but they always decrease as the disease progresses. There may then appear nucleated red cells and the blood condition may approach that of Addisonian anæmia. This is not, however, often the case and the usual type of anæmia is one in which the amount of hæmoglobin is lower in proportion than the amount of corpuscles. The very low colour index of chlorosis is not usual.

It so happens that the author has come across one case in which the red cells were above six million per c.m.m. and there are other such cases in the literature. There was at this time considerable glandular enlargement. This polycythæmia may have no apparent cause or may be attributable to therapy or to the hypertrophy of the red-cell-forming marrow in response to cyanotic complications above mentioned.

The white cell findings are not constant but we can say that as a rule there will be in any but the late stages a slight leucocytosis in which the polymorphs predominate. This may reach about 15,000 and the polymorphs as high as 90 per cent.

In the late stages there is a tendency toward leucopenia but this is not so well marked nor so constant as the leucocytosis.

Certain German authors have supposed that a lymphocytosis is typical of the disease. This means that their definition of what they call pseudo-leukæmia is a disease accompanied by lymphocytosis. As a matter of fact they include a large number of atypical cases of lymphæmia under the title pseudoleukæmia and the disease to which they give that name is not a clinical entity but a group which includes different diseases of which Hodgkin's disease is only one.

There is a relative lymphocytosis and even an absolute increase in small mononuclears in some cases and this is usually assumed to coincide with that period of the disease in which the lesions are comparatively cellular. That this is certainly so has never been proved but there are reasons for supposing that it is an accurate suggestion. In such a case the lymphocytes may reach a total of four thousand per c.m.m. The percentage will vary according to whether there is or is not an accompanying increase in polymorphs.

Perhaps the most significant although not by any means a constant change in the blood is an increase of eosinophils. This is not common in the sorts of disease which are most likely to be confused clinically with Hodgkin's disease. The percentage is not often high but a percentage of 6–8 is one that requires explanation and, failing that, is suggestive of Hodgkin's disease.

The eosinophilia corresponds with the increase of eosinophils often found in the lymph glands.

The serum is said to be more than usually hæmolytic in Hodgkin's disease.

The Spleen.—This is almost always enlarged; not to a very marked extent in the early stages but reaching a great size in some of the more chronic cases.

It is quite exceptional for the spleen to remain unenlarged throughout the disease. As a rule it can be palpated with little difficulty but the enormous enlargement of leukæmia is not very often met with. The surface is also less smooth than in the latter condition.

Symptoms referable to the spleen, such as perisplenitis may give rise to, are not common but the spleen may be tender on palpation as may also the liver.

Histologically the spleen shows varying changes according to the stage of the disease.

To the naked eye it often has a very characteristic appearance and to this the name of "hard bake" spleen has been given. The spleen substance is of a reddish brown colour and all over the surface are studded areas of a white colour and of a slightly translucent appearance. These are usually discrete but may be confluent and are small in the majority of cases. An average size is from 1/8 to 1/4 inch diameter.

On section similar nodules are seen in the interior of the organ.

They are composed largely of fibrous tissue, *i.e.*, of thickening of the largest and smallest trabeculæ. In their meshes are small numbers of lymphocytes and endothelial and giant cells.

Lymphatic System.—It is here that the symptoms of Hodgkin's disease are most manifest. As already mentioned it is the common experience that one group of glands is first enlarged and that no others may show changes for as much as three or four years. Of these groups the cervical and often the axillary of one side are in many instances the first to suffer. The other side of the neck is perhaps affected to a less extent but the glands there may be only discovered on palpation.

When the enlargement is symmetrical from the first the appearance of the patient is very striking—he appears to have no neck—the skin falling straight from the edge of the lower jaw to the line of the collar if he be able to wear a collar. Further examination will often show that the supra-clavicular fossæ are quite filled up and that the episternal notch is also indistinguishable.

This appearance is also seen in other cases of glandular disease of the neck but not so often. There may be enlarged glands in the other sites where aggregations of lymph tissue occur. The axillæ are most likely to be affected but the groins may also show considerable swelling and the mediastinum is seldom free from growth.

The glands may feel either hard or soft; the harder they are the more probable is it that the disease has existed for some time. Although the hard glands are most typical it must be remembered that soft glands by no means exclude Hodgkin's disease and are not a sufficient warrant for an alternative diagnosis of tuberculosis or lymphæmia.

The glands are typically discrete and the whole mass formed by them is irregular in outline and to the touch.

When a second group of glands is attacked it commonly enlarges more rapidly than the first and such "spread" of the disease is usually preceded by a period in which the primary group has become distinctly larger in a short time. The patient may when first seen present a generalised enlargement of glands and be unable to say that any one group was enlarged before another. This is usually the case in acute lymphæmia but in the chronic form of the latter disease a history similar to that given in Hodgkin's disease is not uncommon.

During febrile periods the glands may undergo sudden changes, enlarging as the fever reaches a maximum or after it has been present for a few days and regressing as it falls. This applies to the periods of recurrent fever seen in some cases but may also be noted when there is a single attack of marked pyrexia. Changes in the glands depending on variations in a low continuous fever are seldom sufficiently marked to call for comment.

There are certain changes in the glands which can be appreciated clinically and must be mentioned before the histology is discussed. The fact that they may be either hard or soft has been already mentioned. In the acuter stages they may be tender and the skin over them red and apparently inflamed. No doubt the rapid stretching of the skin accounts in part for this, but it is easily mistaken for bacterial infection. The underlying glands may be quite soft to the touch and the diagnosis is then hard to avoid.

This diagnosis is further suggested when there is, as there may be, a positive tuberculin reaction. The point is that Hodgkin's disease seems especially to predispose to tuberculosis so that both may be present and are so in a large number of cases.

The morbid anatomy then shows features of both diseases but the signs of tubercle are quite distinct from those of Hodgkin's disease. In very few cases are they so blended as to give rise even to temporary difficulty in histological diagnosis.

The glands may break down when tuberculosis supervenes but this although a not uncommon change seldom reaches such an extent as to be appreciable clinically or to call for surgical measures. Very rarely the glands are secondly affected by pyogenic organisms. These may be found in the glands after death but then represent as a rule a purely terminal affection.

Excision of the glands has often been undertaken and on the whole the effects are good. There is no question of the cure of the disease by this means but there is usually a good prospect of relief and possibly of prolongation of life not alone by the removal of local disabilities due to pressure of the glands but from the fact of the removal of what appears to be the primary focus of the disease. Hodgkin's disease runs so variable a course, as do also the other generalised affections of hæmopoietic tissues, that one cannot with confidence assert that the progress of the disease has been delayed in any particular case by surgical measures but the impression that this may be so is probably justified.

After excision the wound almost invariably heals well and the patient often improves in health. Recurrence which may be looked upon as the rule may occur locally or in some more distant set of glands. Local recurrence is common and is easily explicable as one knows that it is quite impossible to remove all the glands in the neck in this or any other disease—unless the patient be disarticulated from his thorax. There is also to be reckoned with the tendency for lymph tissue to grow up in any mesoblastic tissue—a tendency already mentioned as particularly typical of the diseases allied to Hodgkin's but also, of course, known to occur in other morbid entities.

Recurrence may be delayed for some years, but this cannot be counted upon, as more than a year's delay is not very often noted. This fact might seem to contra-indicate operation, but this is not the case inasmuch as operation is not performed in the hope of curing the disease but for the relief of local symptoms which cause considerable discomfort or are even dangerous to life.

During a recurrence the glands may reach the same size as was formerly the case and a second operation may be necessary and as successful as the first.

When the stage of general and marked enlargement of glands is reached operation is no longer of avail except in urgent cases of dyspnœa, etc. A slight general enlargement with great hyperplasia in one situation is not of a similar significance. But generalised and considerable overgrowth is so likely to be soon followed by severe anæmia if that is not already present that operations of any sort are to be avoided if possible.

The histology of the glands is striking and characteristic and shows in its various features a progress of a definite nature. In the earliest stage there is some lymphoid proliferation and the gland appears somewhat similar to that of a case of lymphæmia. On closer inspection there is seen to be associated a varying degree of proliferation of large mononuclear cells with oval and "netted" nuclei. These are the endothelial cells and are similar in origin to the cells of the finer parts of the reticular supporting tissue. It is probable that they are not very distantly related to the lymphocytes. However this may be, the proliferation of lymphocytes is best regarded as a non-essential part of the disorder. It may be reflected in the blood by a certain degree of lymphocytosis (vide page 116) and is perhaps a secondary effect of the endothelial proliferation—just as, for example—red-cell proliferation in the marrow is usually associated with some degree of leucocyte increase which is as far as we know purposeless.

The endothelial proliferation increases and certain peculiar cells occur apparently as direct derivatives of the endothelial cells. These are giant cells and they differ from the giant cells of tuberculosis in various particulars. In the first place they are formed by proliferation of the nuclear part of the cell without division of the cytoplasm whereas the tubercle giant cells are commonly supposed to originate in fusion of cells originally distinct. Whether this be so or not they also differ in appearance. In the tubercle cell the nuclei are usually arranged peripherally and are many and small. In Hodgkin's disease one does not expect to find more than a few cells with more than a half dozen nuclei and a type with two or three nuclei is much more common. These nuclei frequently show mitosis and are larger and less regular in shape than those of the tubercle cell. An illustration makes these points much more plain than enumeration of the differences.

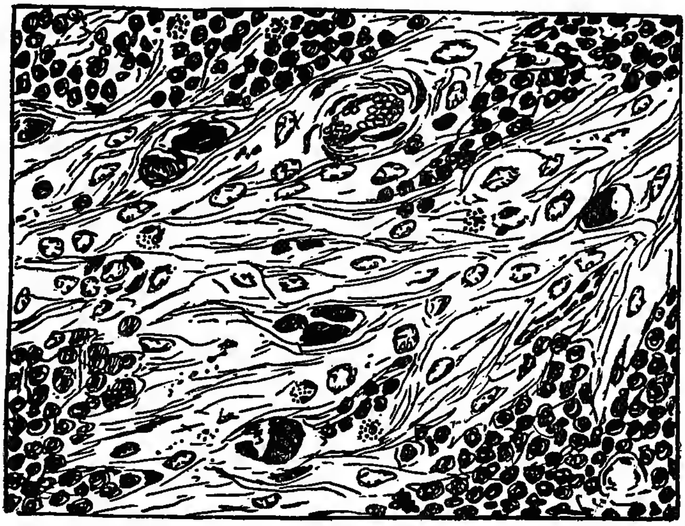


FIG. 22.—Histology of gland in Hodgkin's disease. (Drawn from a specimen by the author.) Showing in the centre a giant cell with three nuclei and surrounded by fibrous tissues with which the endothelial cells seem to be incorporated. There are also in the meshes of this fibrous-endothelial tissue some eosinophils and at the margins of the illustration are less affected portions of gland tissues showing many lymphocytes.

Later a fibrosis which has been already present in some degree begins to predominate amongst the glandular changes and eventually may proceed to such an extent that the gland is almost entirely composed of fibrous tissue. Between the strands are small collections of the endothelial cells and often of eosinophils and lymphocytes.

The lymphocytes are, however, long before this stage definitely decreased whatever may be the condition at the commencement of the disease. The significance and the origin of the eosinophils are alike unknown. They are not always present and may be present in some lesions but not in others. They are less common in the early lesions but may nevertheless be very plentiful even in these. In numbers they vary very much, thus in some cases it is difficult to find any and in others the whole field is dominated by them. They are both mononuclear and polynuclear. They may show mitotic figures. This last fact points to their local origin but the matter cannot be taken as quite sufficiently proved.

The changes in the glands in no case transgress the capsules although the latter may be slightly thickened.

Finally it may be mentioned that all stages between the endothelial and the giant cell are to be met with, that plasma cells are not uncommon and that the changes of tuberculosis when superimposed are accompanied by their own characteristic lesions.

Osseous System.—It has already been mentioned that there are very occasionally periosteal nodules. These have little practical importance in view of their extreme rarity but from a theoretical point of view are interesting as bringing the disease into line with its relatives, myelæmia and lymphæmia.

Respiratory System.—This is rather frequently affected owing to the large proportion of cases in which the glands in the neck are diseased. The results are those of pressure in most cases, *i.e.*, there is diminished air entry clinically and all sorts of changes may ensue in consequence. Collapse of the lung may occur, bronchitis, œdema, and hæmorrhagic œdema. Among the symptoms are cyanosis and dyspnœa—which may be intermittent.

An uncommon complication is pleural effusion. Perhaps one should say that it is uncommon for this to be apparent and to require treatment during life for it is as a matter of fact quite frequently found after death. There are often pericardial and peritoneal effusions as well. These may rarely be chylous.

As was seen to be the case in leukæmia the upward enlargement of the spleen may produce deleterious changes on the lung of the left side. Less commonly the same thing may occur from enlargement of the liver; the right lung, of course, being in this case affected.

Alimentary System.—This is subject to a great variety of disorders in those afflicted with Hodgkin's disease. There are two which are of more frequent occurrence than the others, viz., diarrhœa and ascites.

The diarrhœa may be part of an acute attack or exacerbation of the more usual chronic form. It is then likely to disappear as the temperature falls. It may also be due to disturbance of the lymphoid growth in the intestine which may be implicated in the disease process and secondarily ulcerated. In such a case the diarrhœa is likely to be very troublesome. These are, however, uncommon cases.

It must be remembered that there is, in this disease, a special liability to tuberculosis and the cause of diarrhœa may as a matter of fact be the presence of tuberculous ulcers. In one reported case the patient died from the perforation of such an ulcer.

Ascites has been noted as the first sign of the disorder and its precise cause is not always very plain. There may be no obvious involvement of the liver, in fact, marked changes in that organ are rather the exception than the rule. It is very rarely chylous. It may necessitate frequent tapping.

The presence of lymphatic glands in the abdomen leads, when they become enlarged, to a variety of symptoms. If there be no other glandular enlargement in other parts of the body the correct diagnosis may be impossible to make until after death.

It would serve no useful purpose to detail the various symptoms which may occur—most of which have been met with in one or another case. The hypertrophy of glands near the liver may press on the ducts and so give rise to jaundice, adrenal sufficiency may be seriously disturbed and the mass of glands pressing on the spine may cause sufficient erosion to allow of pressure on the cord and consequently paraplegia. All these have been reported and are adduced as instances of the wide variety of symptoms which may be met with.

The Liver.—Seeing that we are dealing with a generalised affection of blood-forming tissues we should naturally expect the liver to be involved. We may further expect to find in this organ a reproduction of the lesions found in the glands and marrow and that these lesions shall be present especially in the capsule of Glisson. We may also say that even when the lesions seem to transgress the boundaries of Glisson's capsule it will be due to their having arisen in prolongations of the fibrous tissue between the liver lobules and even between the cells of the liver.

That the liver may be involved in the manner above suggested is undoubtedly true but as a matter of fact this is not invariably the case. It has been pointed out already that Hodgkin's disease is necessarily dealt with after the leukæmias for the reason that it is what may be called a less developed type of generalised hæmopoietic affection.

The liver would seem to be affected rather late in the chronic cases and not very often in others except the very acute. It is only in a minority of cases that the white nodules seen in the spleen are present. The liver when normal to the naked eye may show microscopical changes.

The liver may be enlarged but this does not mean that the histological characteristics of Hodgkin's disease will necessarily be found in it.

It may also be tender and there may be attacks of perihepatitis. The two do not always co-exist. Jaundice may be present as the result of pressure on the bile ducts but seldom if ever as the result of intra-hepatic changes.

Urogenital System.—This is normal in most cases. In a few there are nodules similar to those met with in the spleen, etc. There may of course be signs of intercurrent disease such as chronic nephritis and this is not seldom the case. There are even grounds for supposing that nephritis is unduly frequent considering the age, etc., of the patients.

The Skin.—In none of the diseases of this group is the skin so frequently affected as in Hodgkin's disease but it must not be supposed from this that affection of the skin is necessarily common in the experience of an individual. It must also be premised that purpura is not included in the above generalisation.

One of the most distressing features of the disease is pruritus.

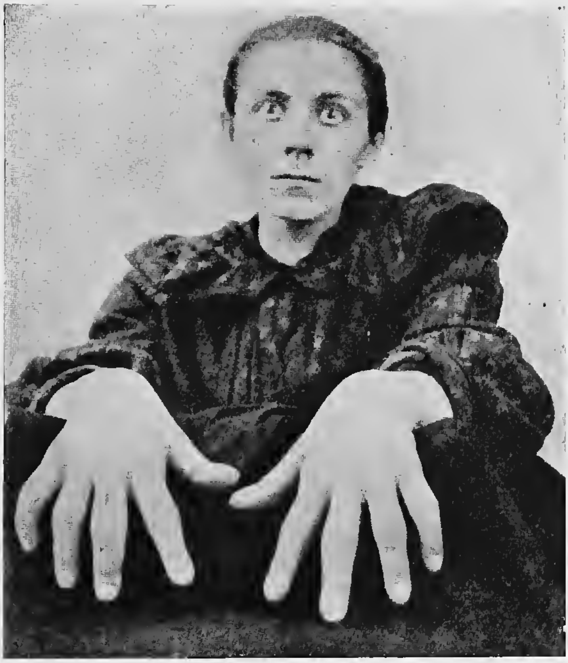


Fig. 23.—A case of Hodgkin's disease in which the mediastinal lymph glands were chiefly affected. Shewing osteo-arthropathy of the hands. So-called pulmonary hypertrophic osteo-arthropathy. (By kind permission of Dr. F. Parkes Weber.)

It is fortunately not very common. It is universal and persistent and may herald the advent of nodules in the skin—these have a structure similar to that of the glands but as a rule in the early stage of growth and showing only a small amount of fibrosis. There are usually many of them and they are sometimes slate in colour, sometimes red and sometimes yellowish. The unaffected skin may be normal in appearance except for scratch marks in some cases or it may have a harsh dry appearance. In two cases seen by the writer there was exfoliation of considerable portions of the epidermis such as may be met with in scarlet fever in which the skin may desquamate perfect casts of the fingers, etc.

Other skin lesions are also met with and these include obviously secondary affections such as may be produced by scratching, intercurrent affections and some which are rather difficult to place. Thus leukoderma has been noted and pigmentation of various degrees. This, in some cases, may depend on adrenal insufficiency, rarely from actual involvement of those organs in growths and less rarely from pressure of glands on the adrenal vessels.

Œdema is not uncommon either in the terminal anæmia and heart failure or from pressure of enlarged glands on large vessels such as the iliacs or brachials.

Purpura is almost always a terminal symptom and is not different from purpura in other diseases of the blood.

Glands Other than Lymph Glands.—The adrenals have just been mentioned. It is not common for the ductless or the salivary glands to be affected in this disease although following the parallel of the leukæmias we should find now and again a case in which there was a symmetrical enlargement of some pair or more of these glands. The mammary glands have been found affected.

Course.—This is very variable as has already been shown in previous pages. The acute cases may run their whole course in less than a month but the majority of cases of this type last nearly a year.

The more chronic cases may endure from two to seven years after the first lesions appear and before a second group is involved. The further course may still be three or four years but is commonly much less—often under a year.

There may be remissions as in the leukæmias but generally speaking one can say that after some group other than that first affected is involved the course of the disease is steadily down-hill.

Remissions.—These may be brought about by treatment or occur spontaneously. They are characterised by diminution in size of the glands and improvement of the general well-being. Sepsis would not appear to have the same effect in producing remissions that has been noted in leukæmia.

Diagnosis.—The only absolute method of diagnosing Hodgkin's disease is by the microscopical examination of an excised gland. It is, however, possible to give a confident and almost certainly correct diagnosis on clinical grounds alone in many cases since the course of the disease is very characteristic as are also many of the signs and symptoms. Diagnosis, then, involves the exclusion of other diseases and the elucidation of those features which may fairly be called characteristic.

Taking the last first we first note that one group of glands is enlarged and often enormously enlarged, that these feel hard as a rule but are discrete and that at first the general health of the patient does not suffer although later there is severe anæmia.

Secondly we observe the absence of any obviously adequate etiological factor and the fact that there is at one time or another a more or less sudden spread to other groups of glands.

With the glandular enlargement there is often fever and in some cases this may be of a very characteristic variety, viz., in the form of recurrent bouts of fever lasting perhaps three weeks with an interval as long or longer between the attacks. The duration of the attacks and the length of time without one are not typical but the fact of recurrent fever with no obvious basis is often a sign of considerable assistance. This is especially the case when there is no external glandular enlargement.

Other varieties of pyrexia are of course seen in cases of Hodgkin's disease but these do not conform to a particular type and vary at different times and according to whether the case is acute or not.

The only other point of importance is the presence of some degree of splenomegaly—this is not invariable and its absence is in no way against the diagnosis but its presence, is very significant. Eosinophila may be present.

When we come to the question of the diagnosis by exclusion we are met first of all with difficulty owing to the clinical resemblances to tuberculosis and the not infrequent association of the two. Any tuberculin test is useless from the point of view of excluding Hodgkin's disease. Its value in the determination of the presence of tuberculosis is still debated, some favouring one test, some another, while not a few people are inclined to discredit the use of such tests on the grounds that old tuberculous lesions are commonly met with and give the test even when not active. Tuberculous glands tend to break down

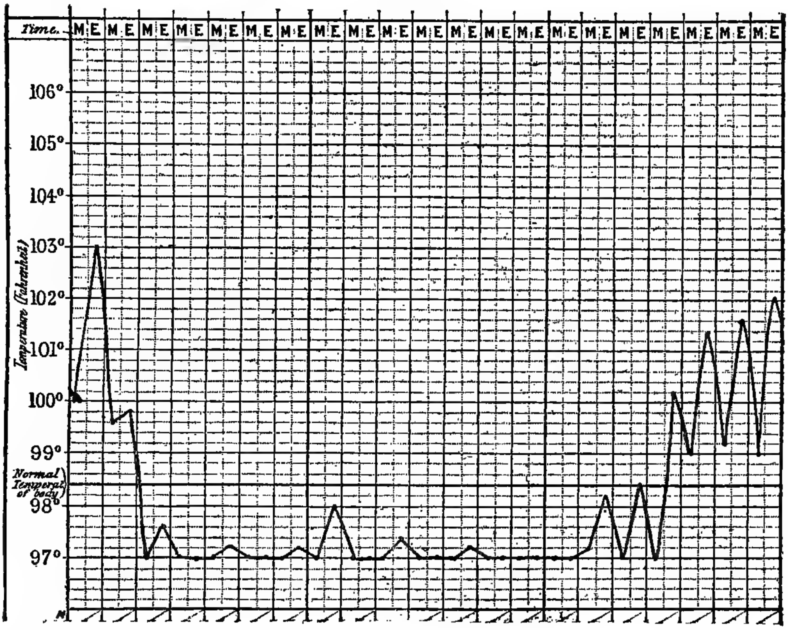


FIG. 24.—Intermittent pyrexia of Hodgkin's disease. Apyrexial period of fifteen days. From the case of a girl aged nineteen.

and to become matted together. There is often a history of some tuberculous manifestation in some other member of the family and anæmia with a very low colour index is common even in early stages.

Generalised glandular tuberculosis more nearly resembles lymphæmia than Hodgkin's disease.

From leukæmia Hodgkin's disease is at once differentiated in the vast majority of cases by a blood examination. It may again be noted that in lymphæmia the total number of lymphocytes or of white cells present is of little importance so long as there are present appreciable numbers of cells obviously foreign to the normal circulation. It may also be recalled that in very exceptional cases of leukæmia there may be no blood changes. In these cases the diagnosis during life from Hodgkin's disease would have to depend on the other clinical features but might in a few cases be impossible.

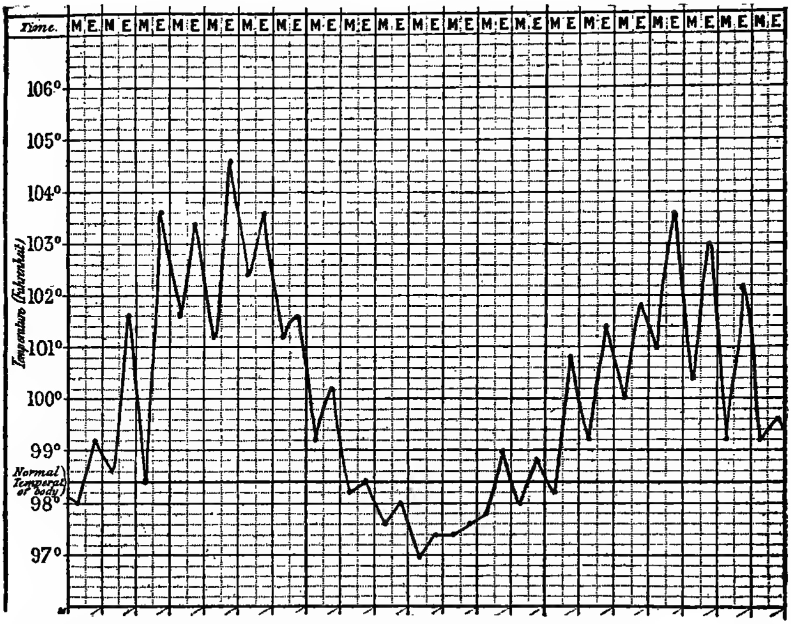


FIG. 25.—Intermittent pyrexia of Hodgkin's disease. Unusually short apyrexial interval of six days only. From a case in a youth of eighteen years of age.

Malignant disease of the glands usually owns a primary focus which is fairly easily identified clinically. There is also absence of response to treatment with arsenic and more cachexia. In many cases there is a larger leucocytosis than is usually met with in Hodgkin's disease.

Lympho-sarcoma of the glands may at first give rise to difficulty but soon shows signs of involvement of neighbouring structures by direct spread through the capsules of the glands. It also forms a more homogeneous tumour and more readily breaks down.

In these days of imperial activity the differential diagnosis of tropical disorders from those which are common to temperate climes is not seldom of importance and this is likely to be more often the case in future years.

Of tropical disorders several are associated with enlarged glands. It may therefore be noted here that much information is often to be gained by puncture of glands with a fairly large needle and subsequent examination of the material which comes away in the eye of the needle or can be drawn into a syringe. In this way the trypanosomes of sleeping sickness are best demonstrated and if there is a possibility of plague or of pestis minor a similar procedure is of assistance. One could in fact point to cases in which plague glands have been operated upon in ignorance of their real nature and in which the operation has been followed by the death of the operator.

Gland puncture seems to be confined to schools of tropical medicine in this country but why it should not be more extensively used is not apparent. It is simple and not nearly as dangerous as puncture of the pleura or peritoneum. The writer does not know of any instance of its being done in a case of Hodgkin's disease but it is at least possible that the appearance of the cells so obtained might be of great assistance. This would be the case especially when there were many eosinophils present. The writer is aware of one case of lymphæmia in which this procedure was carried out with no ill effect.

Syphilitic adenitis will seldom give rise to difficulty and the result of treatment will probably be conclusive even if the history does not help. There is also the Wassermann reaction.

The diagnosis from inflammation of the glands secondary to some septic focus is usually easy but it may be remembered that a history of such enlargement may be present in undoubted Hodgkin's disease and that very rarely there may be septic changes super-added in the course of the latter disorder. Such cases will usually only give rise to trouble in making a diagnosis if they are seen for the first time with a misleading or false history of the commencement of the disease.

Treatment.—As regards radical treatment there is little to be said—it follows that for leukæmia and is discussed on pages 345 and 347 under the headings of arsenic administration and X-ray treatment. There is no curative treatment.

Most of the symptoms must be met with the remedies which are of use in other diseases. As in all diseases of the blood-making organs, the condition of the alimentary tract is of importance. Indeed it is hardly fair to seem to limit attention to the gastro-intestinal system to any one group of diseases but it is certainly the case that no one is likely successfully to treat such diseases as are here dealt with unless he has a working acquaintance with the accepted methods of attaining intestinal asepsis and a lively hope that better methods will some day be available.

For the irritation nothing is of pre-eminent value, but the application of X-rays to enlarged glands seems to alleviate general irritation of the skin. All the usual cooling applications, zinc ointment, lead lotion and the various evaporating lotions will probably meet with some measure of success for a while without giving permanent relief. Carbolic lotion (1 in 20) will sometimes give satisfaction when other prescriptions have failed. It should be dabbed on with pieces of wool.

Surgical treatment has already been dealt with and is indicated as a means of giving relief from urgent symptoms or even from discomfort but is never a curative measure nor one that can be said to retard the course of the disease.

GAUCHER SPLENOMEGALY

Synonyms.—Familial splenic anæmia. Epitheliome primitive. Primary epithelioma of the spleen.

General Pathology, etc.—This disease differs from the others in same group by its frequent family incidence. There are some sporadic cases on record but they form the minority and, moreover, some at least of them have not been typical.

There is no hereditary transmission as far as is known but the disease occurs in more than one member of the same generation.

The morbid anatomy is characterised by changes in the spleen, lymph glands, marrow and liver. All these sites have not been affected in all cases but the whole distribution of the lesions as well as their nature leaves no doubt that they are allied to the diseases here spoken of—generalised diseases of the blood-forming organs.

The most striking and typical change is in the presence of certain large cells with small nuclei and a glassy homogeneous cytoplasm. These have all the appearance of degenerating cells although it must be admitted that the nature of the degeneration is unknown and unparalleled by any common morbid process.

All transitions have been detected between these cells and the normal myelocytes of the marrow. This is of interest as shewing that there is probably a progressive evolutional change as in the other members of this group (see page 49 et seq.)

The lesions have been seen in all the blood-forming organs but the further lesions required to complete the parallel with leukæmia and Hodgkin's disease, to wit, characteristic lesions in the subcutaneous tissue, periosteum, or other mesoblastic structure, are rare. The lymphoid tissue of the intestine has been found affected.

General Symptomatology.—Clinically this disease is splenic anæmia and the symptoms do not differ from those met with in that disease. There is however an added symptom, viz., the presence of pigmentation—usually of the face and extremities. This is of a gold or bronze tint.

Diagnosis.—If the spleen can be examined microscopically there is no difficulty but this is not possible unless it is removed and that again unlikely unless the diagnosis has been arrived at with some degree of certainty first.

Otherwise the fact that there is (1) enlargement of the spleen (2) of familial incidence and (3) accompanied by pigmentation but (4) no characteristic blood changes suffices for the foundation of a diagnosis.

The only disease with which confusion is likely is cholæmia (*q.v.* page 221) in which there is jaundice, urobilinuria, and characteristic blood condition. Splenic anæmia of the usual type is never familial in incidence.

The sporadic case can hardly be differentiated from the ordinary type of splenic anæmia except after splenectomy.

Treatment.—Splenectomy seems to be quite efficacious and should be undertaken early. There is no purpose to be served by prolonging a state of ill health that is curable—so far as the recorded cases go—by operation. If the health is little affected it may be difficult to get the patient's consent and operation must be postponed until the seriousness of the disease is apparent to the patient—but this is the patient's fault and not the physician's.

For the rest symptomatic treatment follows the usual lines. It may be unnecessary to undertake any treatment for long periods at a time.

CHAPTER VII

LOCALISED AFFECTIONS OF BLOOD-FORMING TISSUES

This group is distinguished from the last in that it consists of diseases which affect only one blood-forming tissue or organ instead of having a general incidence on all. It should, strictly speaking, include such diseases as lympho-sarcoma of the glands, myeloid sarcoma and many other malignant growths. These, however, are purposely excluded from the survey of this volume as are all other cancers—meaning thereby new growths infiltrating neighbouring organs, spreading by metastasis and leading to the death of the patient. Such growths as fibromata, lipomata, etc., might also be included but are also excluded as by general consent outside the scope of a book on the blood diseases. We are left with a rather mixed group of which the members may be divided into primary and secondary. Those in the primary group may be considered as comparable to papillomata of a gland epithelium, *i.e.*, as overgrowths of the essential cells of the organ with no tendency to behave as malignant growths. Those in the secondary group include all cases in which there is an overgrowth of the same cells in response to some known stimulus and this group really includes the great majority of cases of blood disorder but for convenience's sake these have to be dealt with under a separate subdivision and this group is left with only one member, *i.e.*, lymphatism. In this disease there is a generalised lymphoid hyperplasia which does not, however, affect any but lymphoid tissue and which exists in response to certain metabolic derangements. It appears comparable to hypertrophy of any tissue in response for increased demands made upon it, *e.g.*, to the hypertrophy of the mammary gland at the time of pregnancy.

Of the first or primary group we have one disease affecting only lymph glands, viz., lymphoma; one affecting only the marrow, viz., multiple myeloma, and one affecting only the spleen, viz., splenic anæmia of adults. The latter is only provisionally placed here for we are not sure of the part really played by the spleen in this disease. The only change of note is pure hypertrophy but there is an increase of fibrous tissue which is also found in the liver and marrow in some cases so that the disease may prove to have important analogies to the generalised diseases of blood-forming tissues. Various etiological questions and a consideration of diseases which may produce very similar changes, *e.g.*, malignant endocarditis, prevent our classifying it with that group at present but the tentative nature of the classification here employed should be recognised.

LYMPHOMA

This would appear to be a very rare disease, the term is applied to an idiopathic and localised hypertrophy of lymph tissue. This has been reported in the case of lymph glands in the groin and of lymph tissue in such positions as the alimentary tract. It is only fair to state that the existence of lymphoma as a distinct disease is not universally recognised. There are, however, cases in which there exists a lymphoid tumour which cannot be looked upon in any other light and for the present such cases must be looked upon as examples of lymphoma in the sense already mentioned.

The signs and symptoms are those of the presence of a tumour and present no particular features of interest. The importance of this disease to the clinician is very little.

MULTIPLE MYELOMA

Synonyms.—Kahler's disease, Bence-Jones albumosuria, myelopathic albumosuria, myelomatosis.

Definition.—A disease characterised by the presence of a diffuse overgrowth of the cell elements of the marrow, and by the presence in the urine of a peculiar product of their destruction and by the absence of characteristic blood changes or metastases.

General Pathology.—The growth seems to start simultaneously in all the bones or the majority of them. It progresses and thins the harder portion of the bones so that they are liable to fracture from very slight trauma and to such an extent that in many cases the pressure of the growth wears away the bony tissue that confines it and a subperiosteal tumour appears. By the breaking or bending of the bones, especially those of the thorax, the carrying out of vital processes may be rendered impossible and death ensues. In other cases a contributory or even sufficient cause is the intense anæmia produced by the encroachment of the growth on red-cell-forming functions.

Either throughout the disease or rarely on some occasions only there is found in the urine a body which has characteristic reactions. Its exact nature is not defined but there is every reason to suppose that it is a product of the destruction of the cells of the marrow growth. At the same time the urine may show signs of excess of salts due to absorption of bone by the pressure of the growth.

Various special tests have to be resorted to for the identification of this body. It differs from ordinary albumen in being precipitated at about 60 degrees centigrade and in redissolving when the urine is boiled. This resolution is not always complete. It is again thrown down when the urine is allowed to cool. With hydrochloric acid it gives a ring similar to that given with ordinary albumen and nitric acid.

Etiology.—It is a disease of maturity and affects men slightly more often than women. There is at present no very great number of cases reported so that these statements must be taken with reserve.

Onset.—This is usually slow extending over one or more years. There have been a few cases of rapid onset and course. The first complaint is often of weakness or of lumbago. Albumosuria can be detected when the patient is first seen in most cases—*i.e.*, if it is looked for. (The term albumose is used without prejudice as to its real nature—a subject too complex for discussion here.)

General Symptomatology.—In the first place there is usually a complaint of pain and weakness and this may continue for four or five years with little change. Then as a rule bending of the spine occurs and this commonly takes place in the upper dorsal region. It causes the head to fall forward and if, as is sometimes the case, the arms are bent, gives a clinical picture similar to that of paralysis agitans although without the tremor. The sternum may be crumpled up as the spine bends. The long bones often escape so that the patient is not necessarily confined to his bed.

Later appears a varying degree of anæmia with associated œdema, etc. Nervous symptoms have also been noted especially of a type usually associated with bulbar paralysis. As there is not always any nervous lesion found after death the cause of the symptoms is doubtful and they are referred to as toxic in origin.

Various associated diseases have been noted.

The urine may be cloudy when passed and is almost always acid. The cloudiness is due to a spontaneous precipitate of albumose.

Blood.—A small leucocytosis has been reported in a few cases but is inconstant. The anæmia has no characteristic features. The cells of the marrow growth are not found in the blood.

Marrow.—Especially in that of the ribs and vertebræ is found the characteristic lesion of the disease. There is a diffuse soft tumour formation which has in places so thinned the bone that the new-formed tissue protrudes externally. It does not, however, infiltrate neighbouring structures. The growth varies from yellow to red in colour. It is composed of cells which differ in different cases but seem to be derived from normal marrow cells and continue to have considerable resemblance to them. In some cases there are a majority of cells similar to plasma cells.

Spleen.—This has been reported as enlarged in one case but the observation has not been further elaborated and it would appear to be a doubtful sign.

Lymph Glands.—These have also been reported as enlarged and even as containing similar growth to that in the marrow. There is some doubt as to the accuracy of these observations. In any case myeloid transformation of the glands might be

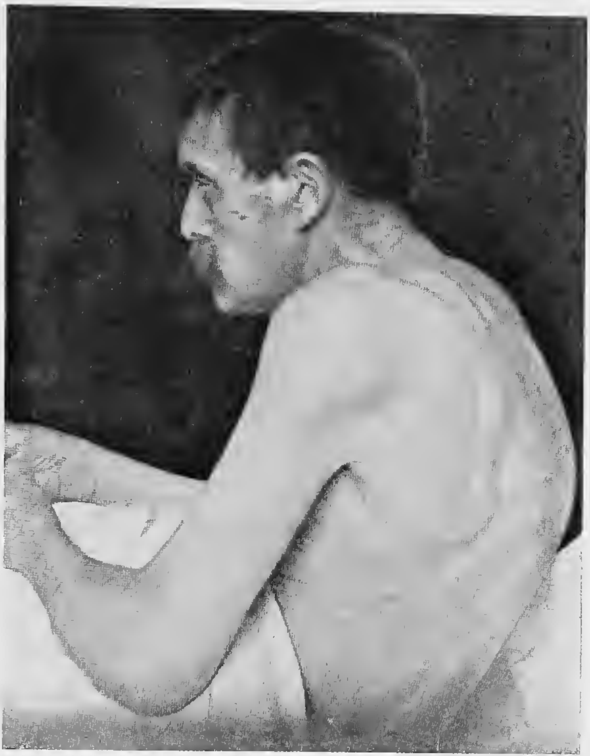


FIG. 26.—Shewing bending of the spine in multiple myeloma. (Dr. F. Parkes Weber.)

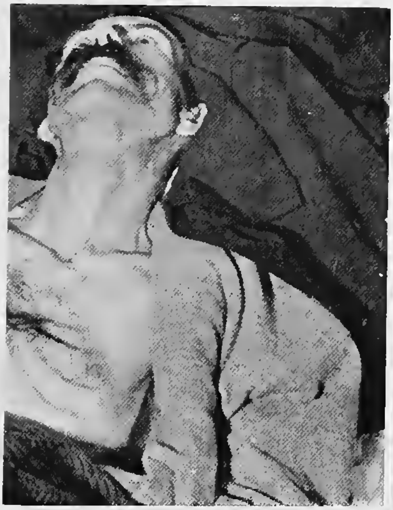


FIG. 27.—Multiple myeloma, shewing sinking in of sternum. (By kind permission of the Editor of the Lancet.)

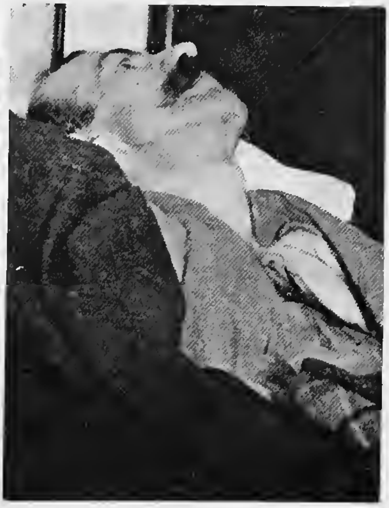


FIG. 28.—Multiple myeloma shewing sinking in of sternum. Also shews position in which head was constantly held. (By kind permission of the Editor of the Lancet.)

compensatory rather than significant of their participation in the primary disease.

Course.—This may vary from a few weeks to eight years or more. One or two years is a common duration.

Diagnosis.—This rests on the finding of the albumose in the urine and the exclusion of leukæmia with which this body is rarely associated (see page 76). The presence of tumour growth on the outside of the bones is of great assistance and the X-rays may give valuable help by shewing the absorption of the more solid parts of the bone even before any fractures or bendings have occurred. The early stages of the disease are compatible with fair health and activity.

Treatment.—The use of arsenic and X-rays may be attempted but no cases of marked relief from these measures are on record.

For the rest treatment can only be symptomatic.

SPLENIC ANÆMIA OF ADULTS

Synonyms.—Primary splenomegaly. Banti's disease. Splenomegalie primitive.

Definition.—A disease characterised by primary enlargement of the spleen, followed at a variable interval by anæmia and often by cirrhosis of the liver with concomitant jaundice, ascites, etc.

Nature.—The nature of the disease is too much a matter of doubt for any dogmatic statement to be risked. The clinical picture is certainly common to more than one condition and may be brought about by, *e.g.*, splenic thrombosis or portal thrombosis, kala-azar, etc. Eliminating these and other conditions which apparently stand in a directly causative relation to the clinical symptoms we have yet a residuum of cases in which the spleen is enlarged owing to factors which we are unable to determine. The morbid anatomy of the organ does not help us much but there is some reason for supposing that we are dealing with a general affection of blood-forming organs as in leukæmia, and some other so-called blood diseases. This is certainly the case in what is known as the Gaucher type of splenomegaly (vide page 130) which presents the same clinical features as that under discussion.

General Pathology.—Apparently the splenic hypertrophy is primary—it is at least as far back as we can go with any certainty in tracing the pathology of the disease. Following it we have various troubles which can be ascribed to mechanical effects. These include pain, peri-splenitis, hæmorrhage in the portal area, jaundice, etc. There is also at the same time some compensatory hypertrophy of the hæmolymph glands but this is not appreciable clinically. Later there is cirrhosis of the liver—at first slight in amount. It is seldom if ever quite absent. Then there comes a degree of anæmia which eventually reaches a severe grade and the patient may die of asthenia. Unfortunately we cannot co-relate either the cirrhosis or the anæmia with the splenomegaly in any satisfactory manner although the clinical course of the disease sufficiently attests their inter-dependence. It will be seen that there is much room for advance in the pathology of this disease—an advance that will hardly be made until we are in possession of more full post-mortem reports on cases of this disease. The minute histology of the liver, glands and marrow is especially required. Portal thrombosis is frequently present but is also met with in erythræmia and in conditions devoid of splenomegaly—there is nothing to suggest that it has any etiological significance.

Allied Diseases.—As has already been mentioned there is some reason to suppose that the leukæmias are allied to this disorder as general affections of the blood-forming organs. It is probable that splenic anæmia is not so truly allied to the disorders which present the same or a similar clinical picture—these are not general affections of the hæmopoietic system as far as we know. Other allied diseases are discussed under Cholæmia on page 224.

Etiology.—Of this we are quite ignorant. It may possibly follow splenic anæmia of infancy.

Age and Sex.—This is a disease chiefly of middle age and is commoner in men than in women in the proportion of three or four to two. Children of ages from four to fourteen occasionally present a similar syndrome but these are precisely the cases in which it is well to think of syphilis, etc.—in fact of known etiological factors. Since these include thrombosis of the splenic vein and since this point is relatively seldom enquired into at the post mortem there is very insufficient evidence for determining the number of cases which occur at about this time.

Onset.—This is almost if not quite invariably very gradual. The splenomegaly is commonly extreme when the patient is first seen and the organ may reach to the pubis before it gives rise to more than the vaguest symptoms. Some acute cases with early onset of anæmia have been reported but their nature is obscure and it is doubtful whether they belong to this group.

Hence the onset from the physician's point of view is often accompanied by such relatively late symptoms as anæmia, ascites, or hæmorrhage.

General Symptomatology.—It is convenient to divide the course of the disease into three stages although these do not by any means represent hard and fast divisions and the last two at least may occur in the reverse order.

The first stage is that of splenomegaly to which attention may be called by indigestion, vague pain or by the observance of a tumour. It is essentially a stage in which anæmia is slight and symptoms few. It may pass without the advice of a medical man being sought.

The second stage is that of anæmia. This is chlorotic in type and of variable degree, but is seldom of the severest grade, *i.e.*, with red cells below one million. All the evils incidental to anæmia are now met with such as dyspnœa on exertion, weakness, etc. Jaundice may occur at this stage although there are clinically no signs of cirrhosis.

The third stage is that of cirrhosis and its attendant symptoms of which a more or less typical facies, jaundice, ascites and hæmorrhages are the most striking.

Fever.—Generally speaking this is an afebrile disorder in all but the latest stages, but as in other cases of anæmia it is not uncommon to find a small evening rise and there may occur a series of distinct febrile attacks.

Nervous System and Special Senses.—These are little affected. The weakness complained of is seldom of a degree to suggest paralysis and except for the occurrence of hæmorrhages the nervous system is exceptionally immune from disorder when one remembers the various ills which may afflict the nerves in Addisonian anæmia and in leukæmia.

Cerebral hæmorrhage is by no means an uncommon termination.

Circulatory System.—The heart is normal in the early stages and shows the effect of anæmia in the later. Congestion of the portal system will naturally lead to some strain on the heart and this will vary in its results according to the degree of cirrhosis, etc.

The vessels are not particularly affected but there has been described a thickening and even occlusion of both the splenic vein and artery. The small arteries in the spleen are usually affected even when the larger escape. In some cases this occlusion of vessels seems to be primary and due to some toxic factor but in others it may have been secondary and in such cases alone is the diagnosis of splenic anæmia satisfactory.

Hæmorrhages especially from the stomach or intestinal tract are often met with and hæmatemesis has come to be one of the recognised symptoms of the disease. These no doubt have a distinct relation to the portal congestion but nevertheless may occur long before this is apparent and may even continue at intervals for many years before the disease reaches a serious stage as far as life is concerned.

Purpura is not common and together with oozing from the gums is almost peculiar to the last stages.

Marrow.—Unfortunately this has seldom been examined at all fully. It shows the slight overgrowth of red-cell-forming tissue that one would expect in any anæmia especially if accompanied by hæmorrhages. In some cases a degree of fibrosis has been met with. The white-cell-forming parts of the marrow vary—in the absence of hæmorrhage there may be a relative diminution of myelocytes and increase of lymphocytes or their mother cells. In the early stages the marrow would appear to be normal.

Blood.—The anæmia is characteristically of what is known as the "chlorotic" type although the relative proportion of hæmoglobin (*i.e.*, the colour index) is seldom so low as that met with in chlorosis. In the later stages all the typical characters of a severe Addisonian anæmia may be met with. This, of course, is so in a minority of cases of all varieties of anæmia and is to be expected to occur occasionally in this.

The anæmia is not extreme when the patient first comes under examination and if it be during the first stage may be absent altogether. When complaint is made of anæmia a count of two to three million may be expected as a rule. This contrasts with Addisonian anæmia in which a count below two millions is commonly met with at this time and agrees more with the state found in myelæmia.

The leucocytes are not affected in the early stages. Later there is a diminution of polymorphs and a relative lymphocytosis or more rarely a leucopenia in which the relative proportions of the cells is about normal. In the final stages a very extreme degree of leucopenia may be reached—the white cells numbering less than one thousand per c.m.m.

A leucocytosis, unless there has been a recent hæmorrhage, is strongly suggestive of a mistaken diagnosis and in any case cannot be explained as part of the disease.

A few myelocytes may occur when the anæmia is severe—this also is common in any anæmic process.

Spleen.—This is characteristically enormous but varies according to the state of the patient and may regress almost entirely if he is improving under treatment.

Its weight and position render the occurrence of symptoms connected with its presence very common. These do not vary from those caused by an enlarged spleen in any other condition.

More important is the chronic inflammation of the capsule which is a not uncommon feature. This is shewn during life both by chronic discomfort due to fibrous adhesions to the diaphragm, etc., and by acuter attacks.

The attachment to the diaphragm predisposes to attacks of pleurisy, basal congestion, etc. Those which drag on the stomach may give rise to a great variety of symptoms especially if this viscus is overloaded. These are aggravated by the cirrhosis of the liver which ensues.

The acute attacks of peri-splenitis may be accompanied by severe and continuous vomiting, by elevation of temperature and very considerable pain. External signs of redness, etc., are not to be expected but tenderness is usual. There may be a feeling on palpation as of surgical emphysema—due to the inflammatory process. Attacks are best treated by hot applications and are usually sufficiently amenable to such measures.

After death the spleen is seen to be large, often with a very much thickened and opaque capsule which may contain definite plaques of hard white tissue of a fibrous nature. The trabeculæ dipping into the organ are similarly thickened and are usually thickened even when the capsule is not greatly affected. The Malpighian bodies are sclerosed and in consequence may stand out as hard white dots from the cut surface.

Microscopically the picture is largely dominated by fibrosis and there is atrophy of both pulp and follicles. The chief incidence may be on the follicles or both may be similarly and equally affected. The other minute features are somewhat inconstant from published reports and do not justify a definite statement except that there is usually some degree of endothelial proliferation and a partial or complete absence of signs of blood destruction, such as cells containing disintegrated red cells or pigment.

Lymph Glands.—With the exception of the hæmolymph glands there is no change which is at all characteristic. The glands are never enlarged to an extent which is appreciable clinically and post mortem seldom show anything but a little fibrosis or congestion. Neither is sufficiently marked to call for further comment.

The retro-peritoneal hæmolymph glands are enlarged, red on section, and microscopically show signs of having assumed the function of the spleen in respect of blood destruction. This is only what one might expect seeing that this seems to be one of their chief functions. Should splenectomy have been performed it is probable that the change will be more marked. The reported cases seldom mention the condition of these glands so that the above remarks are based more on conjecture than on fact although the changes mentioned have of course been seen in a few cases where they have been looked for.

Osseous System.—There is nothing of note.

Respiratory System.—The symptoms are those of anæmia with the addition of those which may be produced by the hampering of the functions of the lung brought about by the presence of a large spleen. The latter will obviously render the action especially of the base of the left lung deficient. Hence one may meet with bronchitis, congestion, pleurisy, etc. Should the spleen be inflamed—the causal organism is not known—the chance of lung trouble is increased.

Hæmorrhage from the lung is rare.

Alimentary System.—The changes here are those of cirrhosis and of traction through adhesions. As a matter of fact they are much more productive of symptoms than of post-mortem lesions. Of the latter congestion and possibly one or more ruptured veins are the chief.

During life the question of the presence of a gastric ulcer may well be entertained especially if, as is usual, hæmatemesis has been a prominent feature. If a proper examination cannot be made such a diagnosis is not likely to be corrected but happily the number of persons who consider an examination unnecessary, when they complain of such a serious symptom, is diminishing. The complaint of indigestion, however, may lead to a course of treatment undertaken in ignorance of the condition underlying the symptoms—and is quite likely to be successful nevertheless, although of course not to be recommended.

Hæmorrhage from the stomach is frequent, melæna less so and epistaxis fairly common.

Liver.—This is commonly slightly enlarged in the early stages and is then more congested than fibrosed. It does, however, show some slight fibrotic changes. It is not as a rule tender or painful nor does it give rise to symptoms until the cirrhosis becomes marked. Then all the usual symptoms are seen, jaundice, an increased tendency to hæmorrhage from the stomach or œsophagus, ascites, and œdema. The cirrhosis may ensue rather rapidly—it never precedes the splenomegaly.

Microscopically in the last stages the liver presents much the same appearance as in alcoholic cirrhosis. The fibrous tissue may, however, enclose collections of lymph cells which are not found in the latter condition although they may be met with in syphilitic cirrhosis.

Urogenital System.—The kidneys are usually cirrhotic, *i.e.*, small, with capsules that do not strip readily and perhaps with cysts. The glomeruli are not particularly affected.

The urine may in consequence show a trace of albumen but there are no other abnormalities which are at all constant.

Skin.—This may show œdema especially of the lower extremities but this is secondary to the cirrhosis or anæmia. In a few cases there is pigmentation and rarely leucoderma associated. These may also be seen in other diseases which present similar features—the writer has seen both well marked in kala-azar—and so are not of diagnostic significance. They are more common in the Gaucher type (see page 130) and may also be due to the arsenic which is commonly given.

Course.—This is very chronic as a rule—cases may endure for ten to twenty years. The larger number of cases last perhaps three years after coming under notice if the degree of anæmia at that time is slight but distinct. It is not possible to make any statement on which it would be safe to base a prognosis in individual cases.

The different stages usually occur more or less in the order given on page 139 but anæmia may occur at any time. In any case the course terminates fatally in the absence of treatment.

Remissions.—These may occur especially in the first stage, in which the health may only be subject to slight lapses from the normal. They occur under treatment or more rarely independent of it.

Clinical Varieties.—These are chiefly those incidental to the age of the patient. Thus a young patient will probably show less adaptability to the occurrence of hæmorrhage and there seems to be an earlier and more constant yellow colour in these cases. This depends in part at least on true jaundice although there is not sufficient evidence to say what change if any in the liver may accompany it. Clinical varieties may also be based on the degree of cirrhosis; indeed Banti's name has been attached to that terminal stage in which cirrhosis is a marked feature. This separate christening is perhaps justifiable clinically but not pathologically. For this reason the name has not been used in the foregoing account.

Complications.—These are hæmorrhages, ascites, etc. They have been already dealt with. Intercurrent diseases do not appear to be common and the patients even appear to be relatively immune from the smaller ills of mankind.

Diagnosis.—This is difficult—in the absence of splenomegaly it cannot be made. Granted splenomegaly there are certain other causes of this condition to be excluded. It is a good rule to examine the blood in any case of enlarged spleen, *i.e.*, if the enlargement is at all prominent and there is not some obvious acute febrile disorder present. A blood examination will in 99 cases out of 100 enable one to exclude leukæmia, cholæmia, erythræmia and splenic anæmia of infants. In the hundredth case in which leukæmia is in an aleukæmic phase, cholæmia lacks the characteristic changes, or erythræmia has but slight polycythæmia the question of diagnosis had better be left over—unfortunately it will be seldom that the physician observes that he is dealing with the hundredth case. He may feel that this is possible if there is leucocytosis, nucleated red cells with slight anæmia, or a count above 6,000,000 red cells per c.m.m. or if the clinical signs are atypical.

A history of the patient not having been abroad will exclude malaria and kala-azar. This leaves the way clear for a consideration of the diagnosis in a fairly early case—when there is cirrhosis the diagnosis is proportionately difficult.

The heart must be examined for possible endocarditis for more than one case is on record in which endocarditis gave rise to splenomegaly, purpura, and all the symptoms of splenic anæmia. Here again the presence of a leucocytosis would assist in excluding splenic anæmia and confirming the diagnosis of endocarditis. If this can be excluded any cause of thrombosis of the splenic or portal veins should be enquired for, especially typhoid and other specific fevers or in women parturition or pelvic disorder.

If these can be excluded enquire for history of traumatism which can apparently cause thrombosis or enlargement of the spleen presumably following injury to that viscus.

Even if these are all negative there remains the question of other primary enlargements of the spleen such as may rarely be met with, *e.g.*, cysts, abscess, infarction, etc., and of secondary enlargements such as deposits of cancer. It is obvious that the above list leaves several loop-holes, for previous histories are notoriously untrustworthy and a man may have been abroad and yet not be suffering from malaria, hydatid, or kala-azar. Moreover endocarditis is not always accompanied by a murmur and even if there is one it may be reasonably ascribed to the anæmia.

The positive features of splenic anæmia must then be taken into consideration and of these long duration is one of the most important. The presence of hæmatemesis is certainly suggestive, as is also leucopenia but generally speaking the positive features are not so reliable as one might wish for.

If there be cirrhosis when the patient first comes under treatment the diagnosis is still more difficult for it is quite possible that it will be impossible to say whether the cirrhosis or the splenomegaly occurred first. If this point cannot be cleared up it is necessary to eliminate factors which can cause cirrhosis and the various forms of that disease. Alcoholism and syphilis must be excluded if possible. Hypertrophic cirrhosis will probably present a larger and more irregular liver than splenic anæmia. Rare varieties of toxic cirrhosis must be excluded if possible and if not the diagnosis must remain in doubt. Fortunately the treatment does not differ very much although of course the presence of syphilis or alcoholism will point to appropriate lines of treatment.

In tropical countries the diagnosis will be much more difficult for it is then necessary to exclude the presence of various animal parasites or to appraise their probable value as etiological factors if present.

Treatment.—The symptomatic treatment follows the usual lines but there are in addition two methods of treatment which require further notice. These are splenectomy and X-rays.

Splenectomy has been performed successfully in a large number of cases and the patients have been reported as well at varying periods afterward. Although the statistics are not all that one would like there are good grounds for saying that the disease may be cured by splenectomy. The corollary that the fons et origio mali lies in the spleen is not as inevitable as it may appear. It is quite possible that some factor acting through the spleen causes symptoms which could not otherwise be brought about. In leukæmia death is due to disorder of the blood-forming organs but we do not suppose that the disease is necessarily a primary disorder of these organs. Indeed the evidence points all the other way for if the disease were primary, for example in the marrow, it would be hard to explain on any hypothesis at present put forward why the glands, the spleen and the marrow in every bone in the body may be simultaneously affected. It is therefore possible that in splenic anæmia we are dealing with a disease that can, so to speak, only express itself by splenic agencies. Fortunately the spleen is not an organ essential to life and there are the hæmolymph glands ready to take on its beneficent functions without so far as we know assuming those of a malign nature. It may be urged that on the same reasoning the removal of the spleen might benefit those cases of leukæmia in which the glands are not apparently affected and as a matter of fact this may well be the case for although all splenectomies in leukæmia have as yet been fatal they have not been fatal from any modification they produced in the disease for which they were undertaken but from surgical accidents such as sepsis, shock, and hæmorrhage.

However this may be, there is no doubt that splenectomy is a rational and legitimate method of dealing with splenic anæmia. Some authorities seem to advocate putting off such—as they say—extreme measures until there appears some severe anæmia or cirrhosis or other serious manifestation. Certainly these may be held in check for some time by medical measures but it is also to be remembered that the further the disease has progressed the greater is the likelihood of adhesions and in consequence the more serious the risk of the operation. It is not suggested that the need for operation can be indefinitely avoided by medical means so that seems no adequate reason for delaying operation.

It is of course obvious that it is right and proper to give the patient such preliminary treatment for a short period as shall render him fit to meet the shock of operation and a course of X-rays if it diminish the size of the spleen is especially to be recommended.

X-ray applications have not been used for splenic anæmia so often as for leukæmia but as far as can be judged the results are about the same, viz., immediate improvement in many cases which is not maintained and a tendency for the rays to be less efficacious after relapse.

The method of application is the same as for other blood diseases but the rays are of course to be applied over the spleen instead of over the bones.

Finally it may be said that splenectomy should be resorted to early for the risks are then comparatively small and that X-rays have not so far been so successful that we can afford to let the better means of cure wait on the less certain. It must not be supposed that splenectomy is an operation devoid of risk to the life of the patient or that it is always and promptly successful—but it is the only means at all that has been ever successful at present and as such is worthy of the place we give to any specific curative treatment of any disease.

Cirrhosis is not a bar to splenectomy, and may vanish when that operation has been successfully performed.

Otherwise treatment is purely symptomatic.

LYMPHATISM

Synonyms.—Status lymphaticus, status thymicus. The disease is sometimes reported under such titles as thymic asthma, thymus death or thymus tod.

Definition.—A process characterised clinically by hypertrophy of lymphadenoid structures; differing from other processes similarly characterised by the more frequent involvement of the thymus, by the absence of any tendency toward the development of anæmia and by a peculiar liability on the part of subjects affected with this disease to die suddenly.

Nature.—It seems extremely probable that the enlargement of lymphadenoid structures is not of the essence of the disease but rather secondary to some disturbance of metabolism, using this word in the widest possible sense as including toxic processes due to bacterial activity, malnutrition, etc.—in fact, any factor which alters the body chemistry.

These disorders of metabolism being seldom explicable or even identifiable we are not in a position to say whether the liability to sudden death is due to the primary metabolic deficiency or to the resulting lymphatic overgrowth.

General Pathology.—There are certain points which characterise this disease clinically of which the chief are (1) the lymphatic overgrowth, (2) the frequent occurrence of the disease in young persons and in association with thyroid disorders in adults, (3) the liability to sudden death, and (4) the so-called thymus asthma.

A proper statement of the pathology of the disease ought to be able to co-relate these factors. This cannot be done in a way which is beyond question or dispute but a theory can be put forward which is of use in understanding the probable nature and process of the disease.

The lymphatic overgrowth we find in two classes of patient, the young and the old. In the young it is well known that the lymphoid tissues are normally more highly developed than is the case in adult life. We are also aware that glandular enlargement is more frequent and of greater extent in the young as a reaction to disease. This is especially shewn by the readiness with which the spleen enlarges as the result of infective diseases. We may assume then that lymphatism in children is to some extent an exaggeration of the normal—whether the normal defensive organism or the normal factor in metabolism is for the moment immaterial.

In adults lymphatism is usually associated with some disorder of the internal secretions. It is thus found commonly in exophthalmic goitre and less often in such disorders as Addison's disease and ovarian abnormalities. It is also found in not a few cases of insanity, in most forms of which the whole metabolism of the body has been shown to be severely deranged.

It is seen then that if lymphatism is considered to be the outward and visible sign of some metabolic disorder its known incidence is the more readily explained.

This co-relates points 1 and 2 to some extent. The question of point 3 as to whether the liability to sudden death depends on the lymphatic overgrowth or on some sudden excess of a pre-existing toxæmia is difficult to answer. That some cases die suddenly and others slowly, but without in either case any sufficient evidence that the lymphatic overgrowth was at fault is certainly the case. It is also the case that both sudden and more gradual deaths occur from such causes as pressure on the trachea.

In view of the fact that sudden pressure on the structures in the root of the neck and the upper part of the thorax might cause sudden cessation of the heart and yet show no sign post mortem one is inclined to suppose that death is due to mechanical reasons in a far higher percentage of cases than is usually allowed. A more definite answer can hardly be given.

The occurrence of thymic asthma is less difficult to explain. That an enlarged thymus can cause dyspnœa is very evident. That it can cause spasmodic or paroxysmal dyspnœa (*i.e.*, "asthma") is also not difficult to understand. The thymus is attached above to the lower part of the thyroid gland or may even reach to the hyoid bone. If any sudden change of position should take place the thymus is pulled up and so narrows the upper inlet of the thorax thus causing pressure on the trachea. When we also consider the possibilities of slight increases in bulk due to varying congestion of the organ, especially perhaps under anæsthetics, we are at once face to face with more reasons for the presence of "asthma" than for its absence.

Thus all four points can be co-related to some extent. This is perhaps as far as we can safely go in discussing the pathology of lymphatism.

General Symptomatology.—Beyond those directly referable to lymphatic overgrowth there are few definite symptoms. In children it is common to find the disease in fat and flabby individuals but among adults the thin, active type suffers as much as the plethoric. Some degree of pallor is common.

There may be signs of deficiency in some internal secretion, *e.g.*, absence of menstruation.

Lymphatic overgrowth may be demonstrated in various positions; distinct overgrowth of lymphoid tissue at the base of the tongue is said to be especially distinctive. The author found this present in the only two cases on which he has had the opportunity of making a post-mortem examination but it had not been looked for during life. Enlarged tonsils and adenoids are rather discounted as diagnostic points, especially in children, by their frequent occurrence. Lymphatic glands in the neck, etc., are seldom palpable nor is the spleen usually definitely enlarged. Nevertheless there is usually enlargement of the lymph nodes in all these situations post mortem. The thymus is typically enlarged. In normal persons it reaches its greatest size relative to the whole body at about two years of age and is completely involuted by the age of 14. Very exceptionally it may persist to adult life. The fact that there is an enlarged thymus (it should not be spoken of as "persistent" unless there is clear evidence that it never underwent involution, which evidence will seldom if ever be forthcoming) may be detected in various ways—all more or less satisfactory according to the clinical skill of the observer.

It may be obvious to percussion or if the thymic dullness is not apparent it may be presumed to be exercising some traction on the pericardium (with the upper part of which it is in close connection) if the cardiac dullness is at a higher level than is normal. The upper lobes of the thymus may be felt in the episternal notch or may even be seen to form a protrusion in that position. Probably radiography is the most useful method of demonstrating the thymus. There may be a very obvious shadow but if there is little change the fact that the shadow of the base of the heart is prolonged upwards and has a concave (instead of the normal convex) side to the left is very suggestive.

After death the lymphoid hypertrophy is found to be greater than the clinical signs during life suggested. Not only are the normal lymphatic structures wherever found hyperplastic as a rule but there are often so many glands, for example in the mesentery, that one feels bound to suppose that the disease has called into activity a considerable amount of potential lymphoid tissue that would otherwise have remained latent. Individual glands are not as a rule greatly enlarged and on section are of a pinkish colour. The hæmolymph glands (see page 29) are almost invariably enlarged and dark red on section.

The lymphoid tissue of the alimentary tract may be similarly hypertrophied.

The so-called asthma which is sometimes met with in cases of lymphatism is a paroxysmal dyspnœa due to pressure on the trachea by an enlarged thymus. It varies greatly in degree and may cause sudden death. Persistent dyspnœa may also be encountered, combined with cyanosis.

The Blood.—There is little known about this but it may be noted that in goître there is very often a lymphocytosis and that in about 50 per cent. of cases diagnosed clinically as goître there is lymphatism while in some 50 per cent. of cases of lymphatism there is some disorder of the thyroid. It would seem at least possible that the lymphocytosis of goître is symptomatic of underlying lymphatism.

A diminution in hæmoglobin is usual.

Diagnosis.—This depends on the recognition of the presence of lymphoid hyperplasia and the exclusion of other causes of such overgrowth. Amongst the latter infective disorders of the glands and leukæmia are most likely to give trouble. The presence of hypertrophy of the thymus is the best single sign.

Treatment.—This is mostly directed to the relief of thymic asthma. This may be procured by removal of the thymus gland which is not a difficult operation as it shells out readily from its capsule. Most authorities advocate stitching it to the sternum and not total removal. This precaution is justified on the hypothesis that the gland serves a useful function but the results of total ablation do not seem to have been deleterious.

Partial removal has also been undertaken but is less desirable since the remaining part may give rise to intra-thoracic bleeding.

If symptoms are not urgent X-rays may be employed and are efficacious in reducing the size of the gland. If, as is sometimes the case, it hypertrophies again further applications are called for and must if necessary be continued until the gland ceases to enlarge.

If symptoms are not at all urgent it may be justifiable to adopt a waiting policy in the case of children as the thymus tends to involute as later life is reached.

If any cause for the hypertrophy can be discovered it should be dealt with.

As regards the prevention of sudden death little can be done. If the thymus is enlarged and other than expectant methods are impossible all care must be taken to avoid sudden movements of the head, increased congestion from excessive exertion, etc., and nervous excitement. The latter precaution is to be insisted upon because there are some reasons for supposing that sudden excess of nervous stimuli may be connected with unexpected death.

As regards operations a word is needed. These are to be avoided if possible but should they become necessary the anæsthetic should be chosen with care and its administration performed most carefully—especially without hurry and in such position that there is nothing to worry the patient. That these conditions are commonly unobtainable in many large hospitals is unfortunately the truth, but in cases of suspected lymphatism it should be possible, as it is necessary, to insist on them.

Probably chloroform and ether mixture is as good as anything in the case of children and there should be no struggling if the anæsthetist has gained the patient's confidence beforehand.

Light anæsthesia is to be avoided in all cases as it adds to the risk of shock on the first incision and does nothing to assist the patient.

The recognition of lymphatism during life is so uncommon in this country that there is a lack of material for forming opinions on the subject of anæsthetics and this is in any case a matter for experts. It does not appear that these patients possess any especial susceptibility to the influence of anæsthetics per se.

CHAPTER VIII

INCREASED RED-CELL FORMATION

This a very common symptom—much more common than is usually recognised. No doubt this is due to the fact that the lesser degrees are of little clinical importance. There is every reason to believe that the red-cell-forming marrow is just as active and just as quickly responsive to calls upon it as that concerned in white-cell production. To put it another way polycythæmia is as readily produced as leucocytosis.

It is not generally agreed how much increase in circulating red cells is necessary to justify the use of the term polycythæmia. Technically it may be applied to any number above the normal of five million per c.m.m. It is to be remembered, however, that numbers as high as 7,000,000 may be met with in apparently normal persons and if we say that they are polycythæmic it must be understood that this does not imply that they are suffering from any morbid process. In this volume polycythæmia is used in its technical sense and not as necessarily denoting some morbid clinical condition.

There is one disease of which an increase in the number of circulating red cells is a diagnostic feature and, as far as we are aware, constitutes the primary feature of the disorder, viz., erythræmia.

This is therefore called an example of primary increased red-cell formation.

The other disorders here to be mentioned are all secondary to known causes. They are secondary polycythæmia, blood crisis and post-hæmorrhagic anæmia. The latter is described on page 191 with other disorders which present the clinical features of anæmia. This is for convenience sake but it should be remembered that the underlying lesion is an increased activity of the marrow in response to the loss of blood and not a diminution as in the anæmia of sepsis, etc. As a matter of fact this increased formation of red cells is not infrequently shewn in the blood by an actual excess of red cells but seldom by a greater percentage of hæmoglobin than normal. As in most processes of red-cell regeneration, the hæmoglobin lags behind the red-cell formation.

In erythræmia then we are dealing with a primary and polycythæmic disease but in the case of the others with symptoms which are common to many different processes.

ERYTHRÆMIA

Synonyms.—Vaquez' disease, Osler's disease, cryptogenetic polycythæmia, splenomegalic polycythæmia, myelopathic polycythæmia, chronic cyanotic polycythæmia, polycythæmia vera or rubra, etc. It must be understood that some of these terms have also been attached to cases of secondary polycythæmia and that the list is by no means exhaustive.

Definition.—An apparently purposeless overgrowth of red-cell-forming marrow, reflected in the blood stream by a varying polycythæmia and increase in volume and usually associated with enlargement of the spleen. (Cyanosis is no essential part of the disorder.)

Nature.—This has given rise to much speculation and we remain very much where we were when the speculation first commenced. Firstly it has been regarded as a new growth and has been compared with leukæmia. The author does not believe that leukæmia is a new growth (in the sense of cancer) nor that the analogy holds good. If it were valid one might expect that the red cells would be similar to those met with in leukæmia, *i.e.*, would include many nucleated cells and many large cells with a high percentage of hæmoglobin. This is not the case nor do areas of red-cell formation arise in spleen, liver, etc., or in the glands as this analogy would lead one to expect.

On the other hand the blood condition in erythræmia is indistinguishable from that of the polycythæmia associated with congenital cardiac disease except in that one point, the absence of any identifiable cause. Erythræmia is equally indistinguishable pathologically, except for the splenomegaly, and this even is absent in some cases.

It is therefore possible that erythræmia is in the nature of a compensatory process and is secondary to some factor which prevents the proper exchange of oxygen between the air, the blood and the tissues.

It may be noted that some have supposed that there is some deficiency in the lungs which prevents proper aeration of the blood, others that the hæmoglobin is lacking in ability to carry oxygen, or to pick it up or to part with it to the tissues. Still others have thought the tissues at fault.

None of those views has been proved to more than mere speculation and any diminished oxygen capacity of the blood has been disproved. The truth has yet to be found. For all we know to the contrary the spleen magnifies the regenerative stimulus of blood destruction until a polycythæmia is produced (see page 30).

General Pathology.—The increase of red cells is the primary feature so far as we can tell. This increases the viscosity of the blood and there is an increase of volume in order to relieve the viscosity. To this most of the symptoms would appear to be due. A further mechanical attempt of nature to deal with the difficulty that she has initiated is increased destruction of red cells. This is shewn by the dark colour of the urine and the presence in it of urobilin. Unfortunately the stimulus of blood destruction inevitably leads to fresh blood formation so that we very soon have a vicious circle. The total result seems usually to be inimical to the patient and the polycythæmia is steadily progressive. Arterial degeneration follows the increased blood pressure which depends in turn on the increased heart work necessary to drive round the body the highly viscous blood. This arterial affection often leads to death and the termination of the pathological process. It will be noted that the place of the spleen enlargement in the process has not been noted. This is because no one knows where it should come in. It is not an essential feature for some cases have had normal spleens. On the other hand, the increased blood destruction is not sufficient to explain it, for far more destruction takes place in the hæmolytic anæmias but the spleen is not nearly so large.

The cyanosis is merely a symptom of the polycythæmia following stagnation of the blood due to increased viscosity (see page 279).

Allied Diseases.—We have mentioned the resemblance that this disease shows to the polycythæmia of congenital heart disease. The essential (if it be essential) difference between them is the splenomegaly found in erythræmia. This is a factor whose value we are not able to estimate.

In some cases of cholæmia (see page 221), a disease in which blood destruction is an essential feature, the destruction may temporarily vanish and the marrow (in a state of compensatory hypertrophy already) has it all its own way and produces a polycythæmia. We are then faced with a splenomegalic polycythæmia which without more than one examination and the history might be very difficult to differentiate from erythræmia.

Whether there is any real parallel cannot be said. It has been repeatedly remarked in another sphere of biology that the egg produces the chicken and the chicken the egg. Authorities have not always agreed as to which came first.

Here we see that blood destruction (in cholæmia) produces a polycythæmia and polycythæmia (in erythræmia) produces blood destruction. Here also authorities differ as to which came first.

Etiology.—We know of no factor that can be said to afford any predisposition to the development of erythræmia. The author has not been able to satisfy himself of the bona fides of alleged congenital cases. He has himself examined the son of a patient obviously suffering from this disease and found a polycythæmia present on two occasions. The actual numbers were 6,490,000 and 6,570,000 and the white cells numbered 11,100 and 10,200 on the same days. There were some subjective symptoms suggestive of the disease and his father was certain that the boy was beginning to suffer from the same disease as himself. On the other hand the author has often found as many red cells in apparently perfectly normal persons and the father (who was a poor man) knew that it would be of considerable interest if his son was found to be suffering from the same disease as himself and might lead to sundry fees in respect of exhibition at meetings of medical societies. There is, in fact, no sufficient evidence of a hereditary form of the disease.

Very many etiological factors have been named, such as influenza, the menopause, etc. There is no apparent worth in them.

Age.—In very few cases have the symptoms been noticed before puberty and it is equally unusual for them to be noted after the age of sixty for the first time.

Sex.—The disease is slightly more frequent in the male sex but the difference is not marked.

Onset.—This is usually gradual and in consequence the patient is seldom able to date the onset of the disease with any accuracy. Probably the symptoms in the early stages—such as vague pains in the limbs—are seldom considered to warrant a visit to the doctor. In a fair number of cases swelling of the abdomen is first noted and in some of these an attack of perisplenitis has called attention to the presence of a tumor. Chronic headache and weakness are also common first symptoms. Vertigo, thirst, vomiting, obstinate constipation have been mentioned in individual cases. In a fair number of cases the patient has been noticed by his friends to have an unusually blue complexion, or to be unduly susceptible to cold; but the disease is then far advanced.

Very many cases, perhaps the majority, come to the physician complaining of some nervous disorder.

General Symptomatology.—The patients present a peculiar brick red colour which may deepen to cyanosis. This is especially well seen in the extremities and in the lips and mouth and is more marked when the weather is cold.

On closer examination varicosities and dilatations of the superficial vessels are apparent. These are well seen in the conjunctivæ. Gingivitis, pyorrhœa and caries are common. Pains in the limbs and bones are not uncommon and headache is frequent. The spleen is usually very much enlarged, the blood pressure high and the heart slightly hypertrophied.

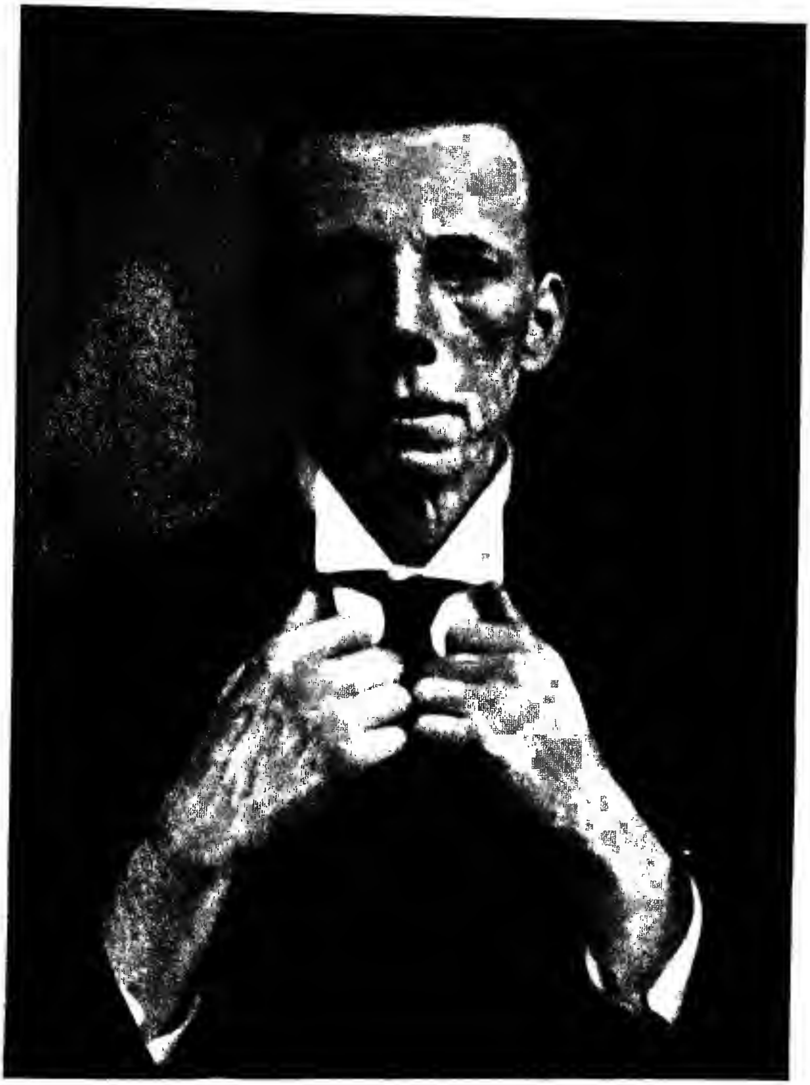


FIG. 29.—Photograph of a man suffering from erythræmia. The red cells were over ten million per c.m.m. Note redness and cyanosis.

Signs of organic disease in other organs are seldom found. The thick dark blood which exudes from a puncture completes the clinical picture, which, in a person over thirty years of age, is almost pathognomonic of the disease.

The Nervous System.—The hyperæmia and congestion of the brain and of the body generally gives rise to a great variety of symptoms.

The simplest is headache—this may be very persistent and is apt to be worse when the patient has been at rest and relieved after moderate exercise. A sensation of fullness in the head, of throbbing, and of giddiness may be met with. Migraine conforming to the classical type is not unknown and acute Ménière's symptoms are not very uncommonly met with. In such an attack the patient may suddenly fall down unconscious and the possibility of cerebral hæmorrhage may well occur to the medical attendant. There may be chronic vertigo and tinnitus, but as a rule an acute attack passes off soon and no further trouble is experienced unless another attack occurs.

Heaviness of the limbs and weakness are almost invariable; there may also occur sudden lapses of memory and almost loss of consciousness. Thus a patient once told the author that when adding up a column of figures he would sometimes all of a sudden lose sight of the figures and become almost oblivious of his surroundings although he never fell down. Then he had to begin his sum all over again.

Actual symptoms of insanity are not very uncommon, although not always sufficient to necessitate the detention of the patient in an asylum. Of these a pathological degree of confusion is commoner in the relatively early stages while dementia may occur later. It is possible that some of these are really cases of arteriopathic dementia.

Peculiar subjective sensations of great variety and even actual pain are not infrequently complained of. Pain in the shoulders, chest, or legs, stiffness and a feeling as if the limbs were fixed at the joints, pins and needles, general aching or impairment of sense of touch may be the most urgent symptoms from the patient's point of view.

The sensation of pins and needles is not at all unlikely to give rise to a diagnosis of neuritis and this has been so in various of the recorded cases. On the other hand the very vagueness of the symptoms may give rise to great difficulty in diagnosis and the result may be that the patient is classed as a neurotic and, perhaps, given an arsenic-containing tonic. The latter has seldom failed to make the symptoms worse.

Erythromelalgia symptoms are dealt with later (page 162).

It is not very often that the subjective sensations are found to have a real basis when tested. Thus loss of sensation although recorded is rarely demonstrated clinically. The knee jerks although they have been absent in one or two cases are usually present and normal in amplitude. The other reflexes are not impaired. Motor loss might be inferred from the complaint of great weakness but although the patient is quickly tired there is no inability to perform any individual movement.

Many of these patients become very apt to dwell on their symptoms and are sometimes irritable to an abnormal extent. There may also be a certain hesitation in answering questions and slightly impaired articulation. Marked sleepiness has been noted.

Cerebral hæmorrhage may be the cause of death and this is rather frequently the case.

Special Senses.—Dimness of vision may be present without any apparent basis. On the other hand it may be connected with retinal hæmorrhages. Optic neuritis is very rare. The examination of the eyes is of the first importance in erythræmia for in them perhaps the earliest signs of the disease may be detected. These consist of hyperæmia of unparalleled extent. The colour of the retina is red but more so than is normal, later it may become very dark red indeed but cyanosis is not to be looked for as a rule. The veins are not only engorged with blood but are very tortuous and may even show varicosities. The arteries are less affected.

The vessels of the conjunctiva are similarly affected but these, being less protected from external influences, are not such reliable guides. They may nevertheless be quite important from the diagnostic point of view. Cases of acquired, or even congenital cardiac polycythæmia do not show nearly so great a degree of engorgement of the vessels of the eyes.

Hæmorrhages into the conjunctiva are not very common but some degree of conjunctivitis would appear to be very often met with. Whether it is really present or is only simulated by the congestion is open to question but the general liability of the mucous and serous membranes to inflammatory disorders makes it quite possible that there is something more than erythræmia present.

Ménière's symptoms and more chronic forms of vertigo have already been mentioned. The acute symptoms probably depend on hæmorrhage into the internal ear (see also under Leukæmia, page 93); chronic tinnitus may be due to congestion alone. It is not often met with. Deafness and otitis media have been reported as associated disorders.

The Circulatory System.—Definite cardiac lesions have been met with in some cases but not to an extent sufficient to explain the polycythæmia. Hypertrophy is the most constant finding. This may be absent if the patient dies while the disease is at an early stage of its evolution but if he dies when the red cells have reached some such figure as 10,000,000 per c.m.m. it is not likely to be wanting. In the same way the blood pressure may be little if at all raised in the early stages and has even been reported subnormal. In the late stages however it is usually raised. This may depend in part on arteriosclerosis which is usually present by then.

Throughout the body the vessels are engorged and the veins naturally suffer most in proportion to their inability to defend themselves. Varicose veins on the legs are very well marked and the usual secondary changes occur in them. Since removal of them would be inadvisable owing to the increased stagnation in the extremities which would result, it is necessary to prescribe a permanent support, *e.g.*, a rubber stocking suitably perforated.

Varicose veins are less marked in other positions but still can be easily detected, especially if the hands be allowed to hang down by the side for a while.

The capillaries do not escape the general stagnation and it is to the changes occurring in them that the cyanosis is due. Increased stagnation in contact with the tissues leads to passage of so much oxygen from the blood that little remains and in consequence a venous tint prevails (see also page 279). Such increased stagnation is an invariable feature of erythræmia.

There are certain symptoms in connection with the extremities which are difficult to explain fully. These are those to which the name erythromelalgia has been given. In the typical form there is intense redness followed by cyanosis of the feet and toes. This is worse if the feet are allowed to hang down. Pain is an important feature of the attack. The attack passes off after a time but further attacks occur with variable frequency. These symptoms do not allow of explanation on a basis of passive congestion alone. There would seem to be also some nervous factor.

Hæmorrhage is not a constant feature of the disease but is apt to occur especially in the form of oozing from the gums. Profuse visceral hæmorrhages are uncommon but when they occur are likely to temporarily relieve the symptoms of the disease. Cerebral hæmorrhage may occur as a terminal event.

It is to be borne in mind that hæmorrhage is seldom easy to deal with in this disease as there is a distinct "hæmophilic" tendency in most cases. However, bleeding never does any harm unless in extremely large amounts.

Thrombosis is reported but not as a very frequent complication. It is difficult to explain its etiology since it is not at all common in the polycythæmia of chronic congenital cardiac disease. Yet the circulatory conditions are apparently the same in the two disorders, *i.e.*, as regards congestion and stasis. Cases have been reported in which very extensive thrombosis has affected all four limbs and has proved fatal from extension to the vena cava. Lesser degrees of thrombosis are rather less rare.

Marrow.—This is the site of the essential lesion of erythræmia, viz., overgrowth—whether it be called hyperplasia, hypertrophy or neoplasm. The normal yellow marrow is an area of undeveloped land but nevertheless good soil. In this disease the red marrow—representing the cultivated area—is carried into that previously lying fallow and, by the time that the disease is well established, there may be three times the normal area turning out ripe red cells.

The bone marrow is congested as are all the other tissues but does not differ much in texture from the normal. It is in bulk that it differs and it is important to remember that the increase in bulk is the cardinal point in the disease, its extent and its variations are not regulated by any physiological need that we can discover.

As a rule the whole marrow—as far as can be gathered from random samples—is affected but in a few cases there have been found areas in which there was no apparent excess of activity.

Clinically this overgrowth is sometimes suggested by tenderness over the bones. This may be elicited by percussion over the subcutaneous portions of the tibia.

X-rays may show an abnormal absorption of the cancellous tissues in the long bones.

Blood.—The total volume of the blood is increased to two or three times the normal in a well-marked case. In the early stages this is probably not the case; but some degree of increase almost always takes place before the patient seeks advice. The increase is appreciable clinically by the dilatation of vessels especially those of the retina.

The red cells vary in number between 6,000,000 and 13,000,000 per c.m.m. The lowest recorded number is 4,500,000 during a remission and the highest 14,180,000 per c.m.m. The latter figure is open to doubt but that figures over 10,000,000 occur is well attested. The author has met with such figures not only in erythræmia but in congenital heart disease and in lung disease.

It has been computed that as many as 13,900,000 red cells could be packed into a cubic millimetre, *i.e.*, if the cells were normal in all respects. In normal blood there is a rather greater volume of serum than of red cells and this contains 5,000,000 cells per c.m.m. so that the computation is probably correct. Such a number ought, however, to render the blood solid and, if the cells were of normal size, would do so. As a matter of fact in polycythæmia the hæmoglobin content is usually diminished and it is at least very likely that the size of the corpuscle is diminished in consequence. This may account in part for the high red-cell counts which have been reported and which, on the rough basis of normal equality in bulk of serum and corpuscles and maintenance of normal size of the individual cell, suggest that the blood ought to be solid if the number of red cells is over 10,000,000 per c.c.m. It is also to be remembered that the red cells are themselves so elastic and give rise to so little friction that their suspension in a fluid medium such as the plasma need not be regarded as essential to the maintenance of circulation.

The red-cell count progressively increases as the time since the onset of the disease lengthens. In the course of remissions or during treatment it may fall to normal. It may also vary according to the part of the body from which it is taken, being greater in a cold than in a warm part.

The hæmoglobin varies as the cells but always at a lower level. It may reach 180 per cent. or more but higher figures are uncommon.

The examination of the blood in a fresh state or of a stained film reveals little departure from the normal except in the occasional presence of nucleated red cells. These are almost all normoblasts and are not often present in any quantity or as a constant feature of the blood examination in any individual case.

A few megalocytes are usually found but the average size of the cells may be below normal.

It will be noted that films from cases of extreme polycythæmia spread very badly owing to the viscosity of the blood. It is therefore well to place a small drop of normal saline on the slide before spreading. This will dilute the blood and ensure that at least part of the film is fit to examine.

There are no spectroscopic changes nor does the serum appear to be different from the normal. It separates out with difficulty but this is to be expected.

The white cells are almost always increased; there are commonly 15,000–25,000 of these and the majority are polymorphs. The eosinophils and mast cells are in the normal numbers and the lymphocytes although relatively diminished are not below normal in total number.

It will be remembered that although the number of white cells in the blood taken for examination should chance to be normal, the total number in the circulation is increased according to the increase in blood volume.

A few myelocytes are often found—they have no particular significance except as shewing that the marrow is working at high pressure.

The Spleen.—Characteristically this is enlarged to a considerable extent. It may reach the extreme size met with in myelæmia and splenic anæmia and cholæmia, *i.e.*, reach to the pelvis and well across the middle line. It must not be forgotten that cases have been reported in which the spleen was not enlarged—as also is the case in myelæmia and cholæmia although we are not aware of any one who has diagnosed splenic anæmia in the absence of splenomegaly. It may also be noted that the disappearance of polycythæmia under treatment does not of necessity indicate any diminution of the splenomegaly although this is commonly the case. These anomalies are hard to explain. Of the many explanations offered none are satisfactory and no useful purpose would be served were they to be recited here.

Clinically the enlarged spleen is usually obvious enough but the patient himself may not notice that his abdomen is increased in size for a long time after the onset of the disorder.

The attacks of peri-splenitis met with in leukæmia and the results of adhesions, pressure on the diaphragm, etc., are similar in the two diseases (see page 97).

Microscopically the spleen shows simple congestion and increased signs of blood destruction in the shape of pigment granules, etc. This is, of course, in addition to the general hypertrophy and consequent increase in supporting fibrous tissue. There are no changes in the spleen which are pathognomonic of the disease. Thrombosis of the splenic vessels is common as it is in other cases of splenomegaly.

Lymphatic Glands.—These are as a rule unaffected except in that they share the general congestion. An exception must be made in the case of the hæmolymph glands which lie on either side of the abdominal aorta. These are usually hypertrophied and exceptionally vascular.

Osseous System.—The only abnormalities of note have been already mentioned, viz., tenderness on percussion of the bones, occasional pain in the bones and absorption of the cancellous tissue revealed by autopsy or the X-rays.

Respiratory System.—Emphysema is very common—almost the rule in these patients. Otherwise the respiratory system is not markedly affected. It is, however, subject to a large variety of disturbances in individual patients.

The general hyperæmia sometimes leads to slight hæmorrhages from the lungs and the viscidity of the mucus makes a chronic and irritating cough by no means uncommon. In addition the congestion seems to favor bacterial invasion although it is not quite clear why this should be so unless it is that the bacteria gain access to the tissues through minute lesions of the mucous membranes which are themselves due to small hæmorrhages. The fact remains that catarrh of all sorts is common and that pleurisy is far from uncommon. This should be remembered when the patient complains of pains not very definitely localised. It is usually amenable to treatment but recurs very readily.

Various diseases of the lungs have been reported as associated with the disease in different cases but not as having any essential part in the disease process.

It will be obvious from the above that breathlessness is a not uncommon feature and is an invariable feature of all advanced cases. It depends both on minor pulmonary lesions such as swelling of the mucosa and upon the cyanosis which is symptomatic of the need for more oxygen on the part of the tissues and consequently gives rise to an increased respiration rate on slight exertion. The stimulus to this increased rate is provided by the excess of CO_2 in the cerebral vessels.

Alimentary System.—The condition of the teeth is seldom satisfactory although it may be doubted whether pyorrhœa and caries are more common in this than in another disease. The gums appear intensely hyperæmic and are often cyanosed.

Ulceration, superficial infection and oozing of blood are very common.

The pharynx is congested as is the rest of the alimentary tract. The condition of the pharynx may be very irritating and lead to frequent attempts to expel the mucus.

Hydrochloric acid has been found deficient in the stomach but this does not seem to be any essential part of the disease. Pain in the epigastrium and flatulence are commonly complained of. They may occur after meals or independent of them. The former is the most usual. Gastric symptoms of this sort respond satisfactorily to treatment in the majority of cases. Vomiting is only troublesome during attacks of peri-splenitis. Other symptoms may also be referable to the enlargement of the spleen but hyperæmia of the stomach mucosa would appear to be the condition most commonly productive of symptoms pointing to this organ.

Diarrhœa is very rare and hæmorrhage from the bowel uncommon. On the other hand constipation is often an important factor in the patient's discomfort. It commonly requires the stronger remedies.

As would be expected from the general congestion hæmorrhoids are not infrequently met with and may lead to a good deal of bleeding—with benefit to the patient.

The Liver.—This is usually enlarged but not always palpable. Signs of cirrhosis and peri-hepatitis are apparently absent.

Microscopically there is intense congestion so that the appearance of the liver is almost that of an angeioma. There is not more than the slightest fibrosis.

The gall bladder is normal, except for congestion.

Urogenital System.—Except for the results of arterio-sclerosis and occasional records of acuter disease there is nothing of note as far as the kidney is concerned. The frequency with which albumen and casts are found in the urine seems to correspond fairly accurately with the probability of chronic interstitial nephritis.

Among common changes in the urine are constant and intermittent urobilinuria, excess of pigments and of iron. These are eloquent of increased hæmolysis but it must be borne in mind that only a very small proportion of the products of blood destruction is excreted in the urine while the remainder is eliminated in the fæces as bile pigment—or altered bile pigment. This fact tends to invalidate deductions drawn from a study of the urinary excretion of urobilin alone.

There are no changes peculiar to the generative organs. The sexual powers are not diminished.

Skin and Mucous Membranes.—The most striking point about the skin is its colour. This, as has already been mentioned, is abnormally red in the earlier stages and only takes on the definite hue of cyanosis later. As in all other cases in which some change in the blood causes an alteration in the tint of the complexion the change is best seen in the lips and extremities and in the mucous membranes.

The cyanosis differs in tint from that of infective met-hæmoglobinæmia and sulph-hæmoglobinæmia but the difference is difficult to define on paper. In the latter conditions the associated pallor makes the blue more distinct and the blue or grey is itself a brighter colour.

The cyanosis is of course worse in cold weather or in any of the circumstances that ordinarily cause cyanosis.

The subcutaneous varicose veins are obvious and when the hands are hung down by the side swell to an unusual extent—an exaggeration of the condition seen in most normal persons whose subcutaneous tissues are sufficiently thin to allow of its observance. Erythræmia cases are not at all inclined to obesity—rather the opposite.

The capillary reflux—the return of blood to an area of the skin out of which it has been pressed—is characteristically slow.

Dermographia has been noted and lesser forms of vasoneurosis are of frequent occurrence. One of these, viz., the absence of a linear red reflex on drawing the finger nail across the skin and its replacement by a white line, has been supposed to be rather exceptional in other diseases; and to that extent significant of this.

Erythromelalgia has already been referred to (page 162). Actual eruptions and recognised diseases of the skin only occur as chance associations.

The functions of the skin appear to be normal.

Course.—Commencing as far as we can see in one of the ways mentioned already, the disease almost invariably runs a slow progressive course with intensification of the symptoms and appearance of some new ones from time to time. There may however be periods during which all subjective symptoms disappear. Even if one of these appears to result from the treatment adopted it is not wise to base a hopeful prognosis thereon; a relapse is unfortunately to be expected.

The disease troubles the patient more in winter than in summer and is better while he can get about. When weakness is so marked that it interferes with proper exercise, the discomfort of the patient is greatly increased.

Duration.—The disease may last from about three to ten years after the patient first comes under observation and an average time is six to eight years. There are however many cases in which the disease certainly lasts much longer than this.

Clinical Varieties.—It is more easy than desirable to make a considerable number of these. A subdivision into those with splenomegaly and those without is supported by some authors; this seems inadvisable inasmuch as it tends to obscure the recognition of a morbid process as against a morbid state. The latter is that which is seen at one examination; the former is that toward which treatment must be directed. The surgeon may often remove a morbid state but the physician is called upon to antagonise a morbid and progressive process, a more difficult and protracted procedure.

Cases without splenomegaly may be early cases in which it has not yet developed, slight cases in which it never will develop or even acute cases in which—judging from an analogy with acute myelæmia—the disease is destined to run its course to a fatal termination before the spleen has time to enlarge. These are not put forward as the actual causes of the non-appearance of splenomegaly but as illustrative of the manifold explanations which may be suggested with some show of reason. In any case until there is known to be some essential difference in the disease in cases with and without splenomegaly there is little use in naming clinical varieties of the disease.

Similarly cases with and without high blood pressure are by some classed apart; here again it is probable that one is separating two stages of the disease and not two varieties of it.

A distinction between those met with in early and in adult life is much more valid for it does not imply that the disease is necessarily different in the two classes nor does it prevent the recognition of differences which, as a matter of fact, will probably be found present to a sufficient extent to permit each variety being considered a separate disease. The question of alleged infantile cases is not yet settled so that this clinical variety may well stand as an important one.

There may be acute cases but they have apparently not yet been noted. The author has seen a well-marked case in which the duration of the disease was said by the patient to be only three weeks but this is by no means the same as saying that the disease did actually first appear so recently.

Complications.—These are thrombosis, hæmorrhages, etc. They are not very frequent.

There is no associated disease which seems to be especially apt to present itself in the course of a case of erythræmia although there seems to be some sort of pre-disposition to inflammation of the serous and mucous membranes. This is in no way so severe as the septic complications of leukæmia.

Diagnosis.—This rests on the recognition of increased marrow activity, *i.e.*, increased output of red cells with no apparent reason and serving no obvious useful purpose. This may be recognised if there be polycythæmia and engorgement of the visible vessels. As has already been noted the retinal vessels are the most reliable guides. Polycythæmia is recognised by the intense colour of the blood which exudes from a puncture and by the small amount of serum which separates from it on standing. If a small capillary or other tube be filled with blood this can be well seen and, although a definite hæmocytometer count is preferable, is very good evidence of polycythæmia.

If there is cyanosis and enlargement of the spleen the diagnosis is rendered more certain and a due consideration of the symptoms assists.

It is, of course, always necessary carefully to exclude heart trouble and lung disorders of sufficient extent in either case to give rise to the same extent of cyanosis but the presence of definite splenomegaly makes it very much less likely that these will be found in any individual case of polycythæmia.

Treatment.—Since the overgrowth of the bone marrow is as far back as we can go in the etiology of this affection, it would seem reasonable to adopt the same treatment that is employed for overgrowth in other situations, viz., surgical removal. As one could hardly remove a great part of many bones in order to destroy the bone marrow therein some measure directed to the destruction of this tissue in situ would have to be adopted. One can imagine that it would be comparatively easy through a small trephine so to disorganise the marrow of a long bone that it would no longer functionate as before. The introduction of a sterilised wire would presumably cause sufficient intra-osseous hæmorrhage to destroy the marrow. This is, however, a matter for the surgeon to decide—so far as the writer knows no such measure has been put into practice. The usual objection to removal or destruction of marrow is that it would grow up elsewhere in a compensatory manner. If, for instance, a bone is destroyed by osteo-myelitis there can be little doubt that some of the spare tissue in other bones takes up its blood-forming duties. This parallel cannot, however, be applied to erythræmia unless one grants that the overgrowth of the marrow is secondary to some physiological necessity for it. This we do not grant as a rule and therefore we cannot assume that destruction of a part of the marrow would lead to overgrowth in some other part—any more than removal of a lipoma from the neck calls into existence one upon the buttock.

The author certainly hopes that some surgical measure will be carried out in a case of erythræmia; it might do no good but on the other hand the patient might greatly benefit (as he does from bleeding—equally a stimulus to red-cell formation) and it is difficult to see how he could be injured by it.

Turning from theory to practice it may be noted that splenectomy has always proved fatal.

X-ray treatment has been employed—the rays being directed to the spleen. The results have been very varied, in some the disease has been made worse, in a few there has followed a striking remission. The opinion of most authors is against it. Nevertheless some weight must be attached to the favourable results.

It is difficult to see why the spleen should be selected as a proper recipient of the rays. It is not engaged in blood formation (*i.e.*, red-cell formation) but in destructive processes and these would seem to be beneficial. Why then hinder them by the use of X-rays? If, as some suggest, a small dose of X-rays stimulates the spleen to greater hæmolytic activity there is good reason for their use but it should be borne in mind that it is only a small dose that is required.

If the rays are employed for the destruction of red-cell-forming tissue the marrow ought to be treated and dangerous experiments in the region of the spleen carefully avoided. The technique of radiographing the bones is given on page 345.

The author therefore recommends X-rays to the bones and not to the spleen in this as in leukæmia—although the two are by no means exactly parallel.

There are certain measures which have been tried on theoretical grounds, particularly on the supposition that erythræmia is a compensatory process. The administration of oxygen or exposure to compressed air is one of these. In either case a lack of oxygen is presumed to be the base of the disease and an attempt is made to supply it in a concentrated form. The results have not been very encouraging but in a few instances the administration of oxygen is of value as a symptomatic treatment—it may be adopted if dyspnœa becomes urgent.

It has been noted that darkness inhibits the activity of the marrow and this has been used as a therapeutic measure. If it held out any prospect of permanent relief one might be tempted to recommend it; it does not and therefore falls into the category of remedies which are worse than the disease.

An iron-free diet would seem a promising mode of treatment but as a matter of fact it is by no means easy to ensure that a diet is iron free and all ordinary foods, or a great number of them, have to be avoided which brings this remedy into a very similar category to the last. Moreover, withholding iron does not decrease the number of corpuscles, although it lowers their iron content.

It has been suggested that one should prepare a hæmolytic serum for those patients—a very dangerous procedure unless it can be guaranteed that the products of hæmolysis shall be expeditiously eliminated. This guarantee can hardly be given.

It has also been suggested that by the injection intravenously of distilled water the blood would be partially laked and the hæmoglobin rapidly eliminated in the urine. This method is less open to objection as we can render the elimination of the hæmoglobin safe by giving sufficient quantities of water by the mouth. The residue of the hæmolysed red cells when the hæmoglobin has been removed wuold give little extra trouble to the spleen. If such ready methods as venesection should be refused this measure might be tried. It would, however, be frankly an experiment.

Venesection has been of great value in many cases and, whether accidental or designed, has usually given considerable relief. This is unfortunately not permanent. Venesection must therefore be repeated as often as the symptoms seem to the patient to warrant it. The physician can hardly judge so well as the patient since the symptoms are largely subjective. At any one sitting about a pint of blood may be removed. Quantities of only a few ounces are of no value at all and only necessitate a more speedy repetition of the procedure.

In cases with low blood pressure bleeding sometimes fails to give much relief but this is not sufficiently often the case to make the existence of low blood pressure a contra-indication to bleeding.

The technique of venesection is simple. The important points are (1) to choose a prominent vein—usually the median basilic, (2) to constrict the arm by a bandage above the site chosen, (3) to cut outward, lest underlying structures be injured and across the vein or nearly across it instead of in its length, (4) to preserve asepsis and to keep the arm raised until the blood has had a chance to clot in the wound when sufficient blood has been withdrawn.

Certain drugs have been recommended as local applications to the spleen or to be taken internally. Mercurial inunction over the spleen seems to have occasionally been of distinct benefit and the various drugs which are said to possess a vasodilator action have met with some measure of success. Of these the nitrites and iodides have especially been employed. They are given in the ordinary doses.

Citrates increase the fluidity of the blood or at least tend to inhibit coagulation and have been used in erythræmia in the form of citric acid or of various more or less pleasing summer drinks. They can do no harm and may be of benefit.

Certain drugs are contra-indicated, especially arsenic and iron; also the aniline compounds and caffeine. Therefore tea and coffee ought to be avoided as far as possible.

Antipyrin although theoretically to be avoided has proved of great value in dealing with the vague pains and discomforts which play so important a part in the patient's view of the disease. Vaquez, who first described the disease, gives small doses, *e.g.*, one or one and a half grains. The salicylates, especially aceto-salicylic acid, are also of value.

For some of the vascular disturbances of the type of erthromelalgia baths of various sorts are useful. Hot douches or hot air may be of great use in promoting the metabolism in the skin and thus in removing paræsthesias, etc.

Exercise is a necessity but must be light and regular rather than heavy and spasmodic. The patient will usually realise this himself.

Diet should be the usual diet of the patient modified by the exclusion of as much red meat as possible. Carbohydrates and fats are least objectionable, vegetables commonly contain too much iron and are thus to be avoided, fruit is less objectionable. It is necessary to bear in mind that refinements of diet are all very well from the theoretical point of view but are often impossible and do not hold out sufficient prospect of marked relief to be allowed seriously to interfere with the patient's enjoyment of life.

The important points in treatment may perhaps be in part judged from the above. Not all the drugs recommended have been mentioned but enough have been noted to satisfy the practitioner that most of them are little better than useless. He will probably do well to pin his faith to exercise, X-rays and bleeding.

SECONDARY OR SYMPTOMATIC POLYCYTHÆMIA

Definition.—The presence in the blood of a greater concentration of red corpuscles than is normal to the individual. Conditions, such as chlorosis, in which there may be actually more corpuscles than normal in the body but which, owing to increase of blood volume, do not show a greater concentration are not included under the heading of Secondary Polycythæmia.

Nature.—This is obviously not a disease per se, but a symptom of a great many conditions some of which are compatible with excellent health.

One of the most obvious functions of the blood is to keep the body supplied with oxygen. The blood is the great internal transport agency.

If for any reason the ability of the red cells to carry oxygen is diminished or the supply of oxygen to them is decreased or the heart fails to send them fast enough about their business, the marrow turns them out in greater numbers and a polycythæmia results.

Moreover, if fluid be extracted from the blood or its bulk be diminished by constriction of the vessels the concentration of the red cells is increased.

Certain poisons too may increase the activity of the marrow as certain others depress it.

General Pathology.—Of this we can say little—possibly because there is little to be said. There is first of all some condition present which demands some degree of polycythæmia if the oxygenation of the tissues is to be satisfactorily controlled. How this factor—which may be one of many—excites the marrow to greater activity is difficult to say. There will certainly be a greater amount of carbon dioxide in the blood than is normal and we know that this gas stimulates, *e.g.*, the respiratory centres. It may also stimulate the bone marrow. Even if we could prove that it did we should have advanced very little for it still requires to be demonstrated how it does it.

Granted that such an effect does occur we have still to demonstrate how it is kept up and whether it is permanent. We can best reply to this that we do not know whether it is kept up by the same stimulus that caused it or by the products of increased blood destruction and that it seems to be permanent just as long as it is required and no longer.

In a word, demand produces supply in this as in other phases of existence and we really know very little more than that.

Of the morbid anatomy more can be said—and will be later; of the pathology time alone can give sufficient demonstration.

Etiology.—This is the most important consideration for our purposes for only by a correct appreciation of the causes of symptomatic polycythæmia can we utilise it as a diagnostic feature. We can divide the cases up in the following manner:

Polycythæmia of high altitudes. It is well recognised that when persons ascend to high altitudes a polycythæmia is evident on examination of the blood and that this disappears when they return to lower levels. This is due to the fact that the air is rarefied in such situations and that the lungs do not at first accommodate themselves to the altered state of affairs. With the assumption of a habitually deeper type of respiration the polycythæmia lessens, but as a rule some remains, since the lungs are not able entirely to compensate for the relative lack of oxygen. The increase in the number of red cells allows sufficient oxygen to reach the tissues. On return to normal levels the polycythæmia is no longer necessary and vanishes.

Cases of laryngeal obstruction. These are on the same footing as those just described since they depend on an insufficient supply of oxygen. Pressure from aneurysm, enlarged thymus, glands in the neck, etc., are here included.

Cases of lung disease. In these there is an insufficient surface for the respiratory exchange of oxygen and carbon dioxide. These include a great variety of diseases of which emphysema is the one most commonly met with in association with definite polycythæmia.

Cases in which the hæmoglobin is at fault. These are cases of coal-gas poisoning, sulph-hæmoglobinæmia and infective methæmoglobinæmia. In the latter two cases comparatively little of the hæmoglobin is affected and the polycythæmia is slight—little more than a suspicious absence of anæmia. In the case of coal-gas poisoning the patient if human usually dies or else recovers before polycythæmia can be established because the conditions under which this disease occurs prevent any regular supply of the carbon monoxide in non-lethal doses. In animals polycythæmia can be caused to appear. This group is therefore of theoretical rather than practical interest, although it is not to be supposed that chronic coal-gas poisoning is unknown among the genus homo sapiens.

Cases in which both lungs and blood are satisfactory but the blood does not pass through the lungs in sufficient quantity. This can only be the case in congenital heart disease and possibly in a few rare cases of patency of the foramen ovale occurring for the first time relatively late in life. This brings us to the subject of the causation of polycythæmia (and incidentally of cyanosis) in congenital heart disease. The above reason accounts for some cases but is not the sole factor in most. Among other facts to be remembered is the fact that the congenitally malformed heart as a rule is acting at a mechanical disadvantage and that therefore what blood does reach the lungs gets there too slowly. The effect of an insufficient rate of flow of the blood through the lungs is further to hinder the proper oxygenation of the tissues and so to increase the need for polycythæmia. A congenital pulmonary stenosis cannot very well avoid hampering the flow of blood through the lungs and is therefore commonly associated with polycythæmia. Furthermore there may be some co-existing abnormality of the lung itself, *e.g.*, collapse of a portion. The subject of cyanosis is considered on page 279.

Cases of acquired heart disease. In these there may be a compensated valvular lesion of a chronic nature when the polycythæmia is merely a part of the compensatory process or a myocarditis when the polycythæmia is more complex. Thus in a case of acute pericarditis with heart failure the author found a red cell count of 7,062,000 per c.m.m. Four days afterward this had fallen to 3,750,000; two days later had risen to 4,981,250, seven days later to 5,810,000, and thereafter as the compensation became adequate remained at a normal level of just over 5,000,000 per c.m.m. A blood crisis was noted to be occurring on the occasion of the first count, was at a maximum on the second and was absent thereafter. On the day of the first count the patient passed only 14 ounces of urine, on the day before the second count he passed 86 and thereafter the amount fell slowly to an apparent normal of about 50 oz. When the patient was first seen his body was obviously failing to excrete fluid and that the blood was correspondingly devoid of fluid is shewn by the high count of seven million odd. Treatment increased his output of urine very markedly—above his apparent normal—and also diluted his blood so that the concentration of red cells was well below normal. Thereafter the urine and the blood both became normal. This case, so far, would appear to represent mere physical effects of the heart failure. But the evidence of blood crisis (see page 183) as witnessed by the presence of nucleated red cell seems to show that the marrow was also active and was endeavouring to make up for the deficient circulation through the lungs by increasing the number of red cells available for carriage of oxygen. The actual activity of the marrow could not be directly demonstrated in this case since the patient recovered but in another case seen at about the same time very marked activity was seen to have followed heart failure. This was a case of tuberculosis of the adrenals with well marked heart disorder. The patient had only felt unwell for 10 days so that it is hardly probable that she had any heart failure before then. She died four days later. The blood count showed 7,025,000 red cells per c.m.m. and the whole of the humerus was full of dark red active marrow as were also the ribs examined. Thus in a very short time there had occurred a very marked reaction of the red-cell-forming marrow and we cannot suppose that the polycythæmia was purely the effect of concentration of the blood—a factor which would seem to have been of main importance in the first case had it not been for the evidence of the second.

Various other cases lead the author to conclude that compensatory polycythæmia occurs very much more readily than is usually recognised and that in consequence a high count in acute myocarditis or acute heart failure must not necessarily be considered evidence of concentration of the blood alone. Actual increase of marrow activity is also a factor. On the other hand chronic heart disease with myocarditis but no failure of serious nature except on undue exertion depends almost entirely on marrow activity for the production of polycythæmia and concentration as a factor is little in evidence.

It may be objected that the above remarks are of no more than theoretical value unless there is some application of them to clinical work. This application the author has come across almost by accident but the evidence he has goes to show that some degree of polycythæmia commonly precedes subjective or objective signs of heart failure, for example in acute febrile diseases. Thus in a case of enteric with little fever and altogether very mild from the clinical aspect—it was only diagnosed after a blood examination which was undertaken on the chance that it might be of assistance—the red cells were found to be 6,540,000 per c.m.m. On the suggestion that this probably portended heart failure the physician re-examined the heart and found it dilated. The patient was not dyspnœic and showed no signs of a dilated heart but care was enjoined and more stringent measures taken to enforce rest, etc., than might have otherwise been the case.

It can hardly be suggested that a blood examination should always be done in cases of acute fevers but this is at least an example of a case which was clinically very obscure and in which the blood examination not only led to a diagnosis (a well-marked leucopenia suggested the propriety of a Widal reaction) but was of material assistance in guiding treatment. We can now pass on to *cases in which the blood becomes more concentrated owing to loss of its fluid portions.* Some of these have just been mentioned, although these are more examples of failure to take up fluid to replace that normally lost than of primary loss. Excessive vomiting, profuse diaphoresis, or diuresis, rapid formation of pleural effusions, etc., all cause a concentration of the blood. Thus it has been noted in stomach disorders, after exercise and in hot weather, in diabetes, etc. It may also be noted that after an attack of polyuria in chlorosis the blood count often goes up and that the same effect may be obtained by treating chlorotic patients in a hot-air chamber.

After large superficial burns there is often a polycythæmia as there is also a loss of fluid. Probably there are other factors at work here too.

Cases in which the polycythæmia aepends on toxic or therapeutic agents. Phosphorus is credited, apparently on good grounds, with causing polycythæmia. Other poisons, *e.g.*, pilocarpine, act by causing loss of fluid. It is not at all uncommon for the anæmia for which adequate treatment has been prescribed to give place for a while to polycythæmia. For example in a case of tuberculosis the author has seen the red cells rise to 6,120,000 under treatment and this is a disease which seldom fails to produce well-marked anæmia.

It is obviously not possible to detail all the causes of polycythæmia but the above may perhaps afford some indication of the large number of diseases in which it may occur.

Symptoms.—These are similar to those already described when treating of erythræmia but there are one or two additions of symptoms not indeed unknown in erythræmia but better discussed here.

Clubbing of the fingers and toes is a common feature of congenital heart cases and may also be met with in various other of the conditions associated with polycythæmia. This is a well-known complication and needs no prolonged mention but it may be noted that it will sometimes disappear if the cause can be removed and that it can occur in the absence of polycythæmia if there be cyanosis present.

Increased susceptibility to cold is a symptom that one would expect and as a matter of fact is seldom absent. Headaches are less common than in erythræmia and are not as a rule marked unless there be high blood pressure.

The polycythæmia does not seem to predispose especially to cutaneous or internal disorders nor, on the other hand, does it seem to confer any immunity as regards them. Varicose ulcers do not occur more often than in other cases of varicose veins and the latter although common when the polycythæmia is well marked—*e.g.*, 8–9,000,000 reds per c.m.m.—are not met with unduly frequently in other cases.

The Blood.—There is little to add to the description given of the blood in erythræmia but there is one marked difference, viz., that while there is usually a distinct polymorph leucocytosis in erythræmia there is not one in secondary polycythæmia unless it owns a cause independent of that which has produced the polycythæmia. Thus polycythæmia may be caused by involvement of the lung in some consolidating process, *e.g.*, pneumonia and the immediate cause of the polycythæmia is the loss of lung surface but the cause of the leucocytosis is the absorption of toxic products due to the activity of the peumococcus.

Nucleated red cells are occasionally met with and this is especially the case in infants. The new-born infant has normally a polycythæmia of about 6–7 million and also a leucocytosis, the former vanishes in three or four days and the latter falls very soon to somewhere about 14,000 per c.m.m.

The hæmoglobin is never as much increased as the red cells and the colour index is accordingly low—0.7 or 0.8 is a common figure for the latter.

Course and Duration.—These vary with the cause and according to the susceptibility of improvement.

Treatment.—The first thing to bear in mind is that treatment may not only be unnecessary but a positive disadvantage. The polycythæmia is a compensatory process—it is true that it is apparently allowed in some cases to proceed to such an extent that the compensation appears worse than the disease—and as such must always be regarded.

In spite of the common opinion to the contrary Nature's remedies very often are worse than the disease; her mode, for example, of dealing with an abscess is usually deplorable, her scar tissue seems to exist in order that it may either stretch or contract to the disadvantage of the patient and all her methods are eventually fatal.

It has already been remarked that patients with intense polycythæmia are much worse if kept in bed. Nevertheless, if the polycythæmia be in the nature of a compensation for, *e.g.*, heart disease, it may be necessary to treat the disease by rest although it makes the complication worse. In such a case the polycythæmia tends to disappear as soon as it is no longer wanted. But it does not always disappear fast enough and in consequence the patient may be put to much inconvenience which timely treatment may remove.

To take a practical example, the author has in mind a man with a polycythæmia of over 10,000,000 which was presumably accounted for by a long history of true asthma and by the presence of emphysema and bronchitis. This man so long as he kept at work or at least obtained a certain amount of exercise was more or less comfortable—he was able to deal with the extreme concentration of his blood so long as the body processes were fairly vigorous. He sought relief for his bronchitis and was advised to keep in bed for a while. So soon as he remained at rest the effects of the polycythæmia became more marked since, no doubt, he was unable to oxygenate the thickened blood and consequently became more cyanosed and more full of carbon dioxide. He was very speedily orthopnœic and gasping for breath. In a few days—he having been spared a cerebral hæmorrhage or syncope—he managed to get rid of his polycythæmia to some extent and was much easier in consequence. Whether he got rid of it by increased hæmolysis or by further dilution of the blood by tissue fluids one cannot say. It is obvious that the proper treatment would have been to bleed the patient when the polycythæmia became more than his altered static condition could deal with.

This is an example of the sort of treatment that may have to be applied even in secondary polycythæmia.

Another example is the common case of a marasmic infant, in fact, a dehydrated infant. The blood is concentrated and the heart fails to work well and toxins are inefficiently excreted. The whole process is intensified in the manner of a vicious circle. By tapping this circle at one point, *viz.*, the concentration of the blood, we can materially improve the whole process. It is not suggested that one can cure it in this way but very certainly that one can give a chance to dietetic measures that would otherwise be futile. Accordingly fluid is injected into the veins or subcutaneous tissue in order to dilute the blood. As a matter of fact the tender age of the patient most often makes rectal injections better to use and these have an additional advantage as cleansing agents. Their effect is the same —the blood is diluted. That this is the case is easily proved by periodical hæmoglobin estimations; as the blood becomes diluted the hæmoglobin is reduced per 20 c.m.m. (the amount of blood ordinarily taken for hæmoglobin estimation, see page 41). Some prefer to take the specific gravity of the blood but this, although not a very complicated procedure, seems hardly necessary.

In this case by treating the polycythæmia we do undoubtedly benefit the general condition and the same is the case in cholera and in many other diseases for which salines are commonly given.

It may perhaps be mentioned that for children five ounces of saline per rectum at a time are sufficient and more may be returned especially if injected too quickly. For an adult a pint is often given without mishap. For children one has given five ounces per hour until the general condition improved—which is often well shewn by the skin and lips becoming moist. In adults there seems almost no limit to the amount of saline that can be absorbed and dealt with. The saline should be from 0.8 to 1 per cent. in strength, *i.e.*, roughly a teaspoonful to the pint of water. It should not be given below the body temperature.

Of course continual saline per rectum is the method of choice but this is seldom practicable outside a hospital or nursing home.

Polycythæmia to which one cannot ascribe any obvious symptoms is best let alone.

BLOOD CRISIS

This term has been applied to a blood symptom. All varieties of anæmia, etc., of which we know the cause present blood symptoms such as diminution in red cells, presence of stippling, etc., but it is convenient to speak of most types of anæmia as if they were separate diseases or at least in association with certain definite morbid processes. We are thus left with a few changes in the blood to which the name blood symptoms may be applied for convenience. Of these blood crisis is one.

A crisis is said to exist when the blood shows a sudden and brief increase in the number of nucleated red cells if these were present before or a sudden appearance of them in other cases. It was originally supposed to be followed by an increase in ordinary red cells but whether this is always so is very doubtful. The author believes that it is a fairly common but not essential part of a blood crisis.

Blood crisis occurs not only in anæmias but in many other conditions including especially those in which the volume of the blood is suddenly altered. Thus the author has seen it more than once in heart failure (a case is mentioned on page 178) and in similar conditions. Reasons have already been adduced to show that it is often associated with an actual increase in marrow activity but whether it is truly symptomatic of that or merely associated with it as it were by accident one cannot say.

The highest number of nucleated red cells that the author has met with during a crisis is 16,000 per c.m.m. In this case which was of a very anomalous nature in other respects there had been about 4000 per c.m.m. present previously. A week later there were only 4000 again but the ordinary red cells had increased by almost a million.

In other cases there has been on one day perhaps only one or two nucleated cells seen, on the next some four or five hundred and on the next and subsequent days none at all. The ordinary red cells have not necessarily varied in number to any marked extent or have even gone down in numbers if there was a previous polycythæmia.

From the practical point of view it may be said that a blood crisis often represents some sudden change in the concentration of the blood. It may or may not be possible to identify the feature on which this depends. If that feature be hæmorrhage it will commonly be obvious, if a fall in blood pressure for some other reason perhaps less obvious.

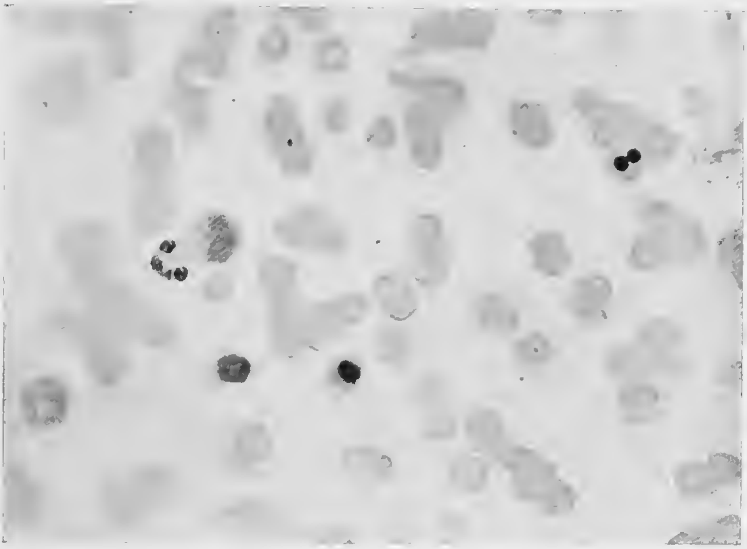


FIG. 30.—Microphotograph of the blood in a case shewing blood crisis. The four cells to the left are respectively a polymorph, a transitional, a large mononuclear and a small mononuclear or lymphocyte. The two cells to the right are normoblasts. The upper one has a dividing nucleus and regular protoplasm, the lower a single nucleus and frayed protoplasm.

A further practical point is that a blood shewing a large number of nucleated red cells must not be considered serious from this feature alone. The author has seen a far larger number after a hæmorrhage than he has ever met with in Addisonian anæmia—in which disease the nucleated red cells have attracted a great deal of attention and have even been elevated into diagnostic points.

POST-HÆMORRHAGIC ANÆMIA

This is dealt with under Secondary Anæmias (page 191) in order to avoid repetition of the many features which it has in common with these.

CHAPTER IX

ACUTE APLASTIC ANÆMIA

A disease has been described under this name which will no doubt be eventually placed among the atrophic anæmias of known origin.

At present the only speculation as to its origin seems to be to the effect that it is a form of Addisonian anæmia in which the hæmolytic agents have destroyed not only the circulating corpuscles but even the capability of the marrow for repair. This may be the case—until we find a satisfactory cause it cannot be proved or disproved—but the age incidence, it affects both sexes from 18 to 28 years, does not support this suggestion altogether nor is there evidence of hæmolysis of abnormal extent. It is true that the hæmoglobin in the body is destroyed or we should find it post mortem, but there is nothing to show that it is destroyed more quickly than is normal.

Others describe the condition as supervening on the anæmia of long-continued hæmorrhage or as following septic invasion. It is not proposed to deal with such cases here—they are mentioned under atrophic anæmias on page 191 et seq. The name acute aplastic anæmia is reserved for a disease of which the etiology is unknown and which runs an acute course to a fatal termination. After death there is found complete atrophy of the bone marrow—it is not this atrophy but its presence in association with a particular clinical syndrome that is here considered to constitute acute aplastic anæmia.

Pathology—About the pathology of the disease we know very little; not many cases are on record and many of these are probably another condition, viz., acute lymphæmia in a terminal phase with severe anæmia. It will often be found in reading over such cases that there is mention of "very slight glandular enlargement" or some other feature which—especially when there has been no post-mortem examination—

makes it quite impossible to accept the case as one of acute aplastic anæmia.

Whatever the cause of the disease may be we are bound to suppose that its chief effect is to inhibit the formation of new red cells by the marrow. Thus as the old ones are removed from the circulation in the ordinary course of things there are none to take their place and severe anæmia results. In a short time the patient dies—usually when the red cells are somewhere about 1,000,000 per c.m.m.

A secondary effect of the anæmia would seem to be degeneration of the vessels such as is seen in other severe anæmias and this is manifested by the presence of hæmorrhages. Purpura is, in fact, a very prominent feature. The gums are swollen and bleeding—probably from septic infection which has been favoured by their low state of nutrition.

There is no tendency toward enlargement of the spleen or lymph glands.

The **course** of the disease is about a month or less and there is no known method of dealing with it. If one accepts the view that it is a toxæmia of bacterial origin or that it is a form of Addisonian anæmia, that opinion would direct the undertaking of the most rigorous measures of intestinal asepsis possible.

The Marrow.—There is in the first place no increase of red marrow and, secondly, according to the time that the disease has been in existence, an actual replacement of the red marrow by fatty tissue. This may show gelatinous change. On microscopical examination the red marrow is seen to be largely composed of lymphocytes and myelocytes; leucocytes and red cells are very scanty. Those that are present may show various sorts of degeneration, *e.g.*, fragmentation of the nucleus or signs of its solution in the cytoplasm.

The Blood.—This is characterised by a diminution in the number of marrow formed cells, *i.e.*, red cells and leucocytes. Those which are present are not abnormal as is the case in *all* other varieties of anæmia. The hæmoglobin index remains where it was before and polychromasia and stippling are not found. There are no nucleated red cells. It must be allowed that the above remarks are a little too absolute as there can be no absolute atrophy of any tissue so far as we know. There are minute signs of activity in scattered foci in the marrow and these may send out a very few cells which are abnormal. In so far as these are present the blood departs from the normal and is atypical. Moreover if the blood was not normal before the onset of the disease the cells would then have shewn some variations from the normal and this would persist.

The diminution of polymorphs gives rise to a striking relative increase in lymphocytes. This may give rise to a mistaken diagnosis of lymphæmia but as a matter of fact it would seem probable that this is an infrequent mistake—the common error is to suppose that so few lymphocytes even though their relative proportion is high cannot warrant a diagnosis of lymphæmia. It may therefore be stated that in lymphæmia the cells present are abnormal and distinguishable from those normally present in the blood (see page 62). The only exception to this statement is that in lymphæmia when a remission with return of the blood to the normal is in process of occurring there may be an excess of normally built lymphocytes before the latter reach their natural percentage. This is not an exception that is likely to give trouble in the diagnosis of acute aplastic anæmia.

The red cells as already stated are often about 1,000,000 just before death but lower figures are on record. There may be only 300,000 to 400,000 red cells per c.m.m. Apparently death does not occur if the red cells are above two million.

Basophilia has been recorded in a few cases.

CONGENITAL ANÆMIA

This is another rare disease. A few cases have been described in which children have been noted to be pale since birth and do, in fact, present some degree of anæmia, although there are no symptoms referable to this abnormality of the blood. Such cases may really be examples of mistaken diagnosis but there is no particular reason to suppose so and the disease may well stand until it is disproved.

The diagnosis requires the exclusion of two other conditions which may also be congenital. The first is cholæmia (see page

221) and will be discussed later, the second is the congenital anæmia sometimes met with in twins or in the more weakly of twins. This is due to the fact that the twin has not obtained a sufficient share of iron to tide him over that period of life in which iron is taken with the food in only very minute amounts. It is readily amenable to iron treatment. It may also be found in children that have been kept at the breast too long. The ready response to iron therapy and the presence of symptoms of anæmia (apart from signs) serve to differentiate it from congenital anæmia.

As a description of these cases cannot be written for lack of material the author proposes in lieu thereof briefly to describe a case which came under his own observation.

The child was a male aged one year and five months and came under observation for the treatment of a nævus. He was well nourished but looked very white. The history was quite clear that he had been pale since birth and was not elicited by leading questions as the information was volunteered as soon as it was apparent that the extreme pallor was exciting interest. The informant was not the mother of the child since the latter was illegitimate and had been adopted almost from birth. The foster mother knew the real mother and was sure that she had good health. The family history was otherwise lacking. There had been an attack of diarrhœa and vomiting about four months previously but no other illness. The child had been brought up on milk chiefly and had not been put to the breast. He was a vigorous baby and much objected to having his ear pricked. There was no yellowish tinge at all. The pallor was as obvious in the mucous membranes as in the skin. The blood shewed:

Red corpuscles	5,925,000 per c.m.m.
Hæmoglobin	66 per cent.
Colour index	0.557
White cells	11,300 per c.m.m.
Polymorphs	25.4 per cent.
Eosinophils	3.0 per cent
Mast cells	0.4 per cent.
Small mononuclears	65.8 per cent.
Large mononuclears	2.6 per cent.

There was anisocytosis with many microcytes and megalocytes but little poikilocytosis. Polychromasia was frequent while stippling was not seen. There were no nucleated red cells found.

From the history and by exclusion a diagnosis of congenital anæmia was made. The patient was under observation for some time but no abnormality developed other than the nævus and the anæmia.

This, then, is the sort of case to which the term congenital anæmia has been applied.

CHAPTER X

ATROPHIC ANÆMIAS AND OTHER SECONDARY ANÆMIAS

Synonyms.—Simple anæmia, traumatic anæmia, post-hæmorrhagic anæmias, hæmolytic anæmias (excepting cholæmia), the anæmia of premature children, senile anæmia (possibly), septic anæmia, tuberculous chlorosis, tropho-neurotic anæmia, many cases styled pernicious anæmia, helminth anæmias, parasitic anæmias, Egyptian chlorosis, bothriocephalus, and ankylostoma anæmia, infective splenic anæmia of infants (Leishmaniasis), myelophthisic anæmia, etc., etc.

Nature.—The above diseases are grouped together in defiance of strict pathology but for convenience as the symptoms referable to the anæmia are the same or nearly the same in all. They readily fall into three classes according to their nature. It must, however, be remembered that a pure anæmia of one of the three types now to be mentioned is not common.

1. *Atrophic anæmias.* In these there is an atrophy of the bone marrow, *i.e.*, an absence of the normal amount of response. We have as types the exhausted response as seen after repeated hæmorrhages and the deficient response seen in some septic cases. A third type is that in which the marrow is generally encroached upon by some growth, *e.g.*, multiple myeloma (page 134) or diffuse cancerous metastasis (see page 361).

2. *Hæmolytic anæmias.* In these the blood is injured while in the circulation and the marrow is in almost every case in a state of hyperactivity attempting to make good the loss. We have as types the severe anæmia of, for example, benzene poisoning and the less severe condition seen in the acute specific fevers and in such diseases as malaria.

3. *Post-hæmorrhagic anæmias.* In these hæmoglobin as such is lost to the body and the marrow is in a state of hyperactivity

attempting to make good the loss. We have as types the anæmia following external hæmorrhage and that of cases of hæmoglobinuria. The reasons for the inclusion of the latter will appear later.

It will subsequently appear that the above division and even the very inclusion of some of the types of anæmia to be described as secondary anæmias is open to objections on the score of inconsistency. From a practical point of view, however, it is thought that this is the most efficient classification.

General Pathology.—This differs according to the variety of secondary anæmia with which we are dealing.

In *atrophic anæmias* the primary factor is usually of a toxic nature and its effect—working mysteriously—is to inhibit the activity of the marrow. Hence results anæmia of varying degree. If the cause can be removed the marrow will as a rule regain full activity but in the atrophic anæmia of long-standing hæmorrhage this return may be very slow and perhaps a permanently injured marrow may be left.

In the *hæmolytic anæmias* the blood is injured in the circulation by some adverse influence that does not necessarily affect the marrow. In any case the morbid influence seems to destroy fully formed cells but not to be able to inhibit their formation. If the poison is very concentrated or gains direct access to the blood stream the cells will show actual fragmentation and the hæmoglobin will in part be converted into methæmoglobin. Hence these patients are cyanosed. The injured cells are removed from the circulation probably in the spleen for the most part and only to a lesser extent in the marrow and glands. Hence there is a great diminution in the number of red cells and an increased activity of the spleen. This activity—again working in a way not known to us—would appear to elaborate from the products of the destroyed cells a very effective stimulus to bone-marrow activity. This is not the same cause of increased activity as that which operates after an external hæmorrhage—we should not expect it to be. In keeping with this is the fact that the bone-marrow activity is equally not the same as that seen after hæmorrhage. After acute destruction of blood by such a blood poison as benzene the marrow turns out red cells of the type seen typically in Addisonian anæmia—the blood is of the miscalled "pernicious" variety.

If the poison acts less acutely the blood regeneration may approach the more common atrophic type and if it acts more acutely the marrow may, as it were, be paralysed—at least for two or three days.

Secondary features in the pathology are the excretion of an increased amount of urobilin in the urine and fæces, purpura, etc.

In *post-hæmorrhagic anæmias* the anæmia is produced suddenly and we have to deal with the repairing processes. Small continued hæmorrhages lead to an atrophic type. The first result of a large hæmorrhage as seen in the blood is nil. There is simply a loss of a volume of blood and the composition of that remaining is not altered. Very soon—in a variable time but less than 24 hours—the remaining blood is diluted by tissue fluids in order that the total volume of circulating fluid may be kept at its proper standard. This would appear to be a very important point and we make use of it in the treatment of hæmorrhage. The blood if examined then shows a paucity of corpuscles and at the same time there are signs of increased marrow activity in the presence of a leucocytosis, nucleated red cells (not invariably), cells poor in hæmoglobin and showing polychromasia. Very often this dilution is overdone and the first estimate of the amount of anæmia is too low. This is very soon rectified by passage back again of some of the fluid into the tissues. We then have to deal with a state of hyperactivity of the marrow reflected in the blood stream by a gradually increasing number of red cells and a rather slower increase of the hæmoglobin. The former, *i.e.*, the increase of red cells is not uncommonly overdone, as was the dilution of the blood, and some degree of polycythæmia may result. In post-hæmorrhagic anæmias there is no excess of urobilin in the fæces or urine nor, as a rule, that yellowish complexion which is equally suggestive of some blood destruction in the body. The latter is only present when the strain is so great or so prolonged that the marrow turns out bad red cells unable to resist destruction before their physiological life is done.

The above, perhaps, gives some idea of what is here intended to be meant by the term secondary or symptomatic anæmia and a definition of the term has been left until now. Anæmia ought by itself to mean a condition in which there was an actual poverty of blood but unfortunately mere dilution of the blood without diminution of any of its constituents or even with actual increase of them gives rise to what is clinically a state of anæmia. It is obvious that to insist on the pathological entity of "poverty of the blood" to the exclusion of clinical "anæmias" in some cases would be of no value. We must then look for some other definition of anæmia before we can even begin to suggest what secondary anæmia should comprise. One might think that the following was adequate, viz:

Anæmia is a condition in which the amount of hæmoglobin available for oxygen carrying is insufficient for the needs of the body.

A moment's reflection will show us that this is the state of affairs in most cases of polycythæmia—this also must be rejected. A modification of it may, however, serve so that we can define anæmia—on a mixed clinical and pathological basis—as a condition in which the amount of hæmoglobin available for oxygen carrying is insufficient for the needs of the body and in which the amount of hæmoglobin per cubic millimetre of blood is less than normal.

Secondary anæmia as distinct from primary should be anæmia of which we know the cause—as a matter of fact it by common consent means something quite different. We do not know the cause of measles or of scarlet fever. In each of these some degree of anæmia is invariably present. We certainly do not know the cause of this anæmia yet because it is a subsidiary symptom we are content to call it a secondary anæmia. We know far more about the cause of so-called "pernicious anæmia" and the features of this disease can be produced by infection of animals with particular strains of the colon bacillus which have been recovered from the fæces of human cases of the disease. Yet this is usually considered a type of primary anæmia which is particularly obvious. Not to labour the question unduly it may be said that in this volume the division between primary and secondary anæmias is not insisted upon for the reason that it is in the main entirely artificial. Where anæmia as a symptom dominates the clinical picture it has been necessary on that as well as on other grounds to describe that clinical picture as a "disease of the blood-forming organs" or a "blood disease." Where anæmia does not dominate the clinical picture or is in association with some other well-marked condition the disease has usually been referred to the secondary or symptomatic group. As far then as any differentiation has been made it has been made on purely opportunist grounds and is not to be taken as based on etiological or pathological differences.

Definition.—Secondary or symptomatic anæmia is an anæmia which owns a definite cause or occupies a subsidiary place among the symptoms of that disease process of which it forms part.

Etiology.—It will be convenient here to expand somewhat the list of causes of anæmia already suggested in previous paragraphs.

Among the causes of atrophic anæmia sepsis takes the first place. It is found to some extent in all the acute specific fevers and is then apt to be complicated with some degree of hæmolysis—as indeed is the case in many other conditions. The sepsis which accompanies cancer often leads to a severe grade of atrophic anæmia and even in the absence of sepsis cancer seems to have an adverse effect on the blood (see also page 360). The effect of the acute specific fevers may be so profound that after death there is extensive fatty change in the marrow just as is seen in the idiopathic aplastic anæmia already described.

Malnutrition, rickets, and various other conditions associated with metabolic abnormality are also productive of anæmia. Probably iron starvation (see page 211) causes the purest type of atrophic anæmia.

The presence of intestinal parasites is well known to cause anæmia, but this may in rare instances be of the hæmolytic type and is in any case probably associated with some dilution of the blood and therefore appears worse than it really is.

Encroachment on the marrow by primary tumour formation or by leucocyte proliferation also produces anæmia—in part at least by physical means, *i.e.*, diminution of the space available for red-cell formation. Secondary tumors such as may follow cancer of the breast or stomach in particular have a similar effect and osteomyelitis and medullary hæmorrhage do the same. In all but the first two cases there is room elsewhere for compensatory hypertrophy as a rule but an exception must be made in the case of diffuse infiltration of the marrow by cancerous growth which has been called osteomalacia carcinomatodes.

The hæmolytic anæmias are much rarer than the atrophic, and outstanding examples are practically confined to cases of suicide and certain industrial disorders. Thus such chemicals as benzene may be taken in large quantities either by accident or on purpose and a typical hæmolytic anæmia results. Similarly workers in benzene factories, in the manufacture of high explosives, and miners are all liable to suffer from inhalation of poisonous fumes. This will not occur when there is an actual explosion for then noxious substances will probably be split up but if they burn slowly fumes are given off which may be absorbed by human beings.

Less marked hæmolytic anæmias are associated with the specific fevers when there is high temperature. The mechanism of blood destruction in these cases is not understood fully. It is not only due to the fever—very likely the toxins are to some extent hæmolytic. The majority of the cases as already mentioned show an atrophic anæmia during convalescence.

Parasites occupying the red cells naturally lead in a great many cases to their destruction and the anæmia of malaria is in part of this nature. There are also certain strains of bacteria which seem to have the power of manufacturing hæmolysins and this is true, as well, of most snake poisons.

Extensive burns probably destroy the blood directly while in the circulation but the anæmia is commonly masked at first by the concentration of the blood which also occurs.

Any cause of hæmolysis acting very acutely may cause atrophy of the marrow and any similar cause acting for a long time or in small doses at frequent intervals may have the same effect. In other words the marrow may be primarily or secondarily exhausted by a poison which in most cases would not inhibit its activity but on the contrary allow of its augmentation under the influence of the products of blood destruction.

Post-hæmorrhagic anæmias follow hæmorrhage either internal or external and the loss of hæmoglobin met with in hæmoglobinuria gives rise to a similar type of anæmia. Thus the causes of post-hæmorrhagic anæmia include external wounds, internal bleeding, hæmophilia and purpura, scurvy, paroxysmal and symptomatic hæmoglobinuria, rarely Raynaud's disease, etc. As in all other anæmias the atrophic type may supervene after a time.

General Symptomatology.—The first point which needs some attention is the question of how far one is justified in diagnosing anæmia solely from the presence of pallor. That this is not always possible is well known. In the first place one patient may have anæmia and no pallor and another pallor but no anæmia. The first class of case is usually mentioned in text-books with a warning that some cases of chlorosis and "pernicious" anæmia may show a rosy flush on the cheeks which tends to obscure the presence of anæmia. The author has seen such cases but believes that there is little excuse for making such a mistake if the mucous membranes be also examined—the lips are of a pinkish colour quite different from that of the normal complexion but somewhat resembling that seen in the artificial complexions assumed by some of the fairer sex. On the other hand pallor may be present and obvious in mucous membranes without any apparent reason for doubting the existence of anæmia—although the latter is not found on examination of the blood. The author once examined the blood of a girl who was so pale that she had for a long while been given iron by disinterested physicians. The hæmoglobin percentage was above 100 but there was nothing about the patient's appearance to indicate that this was the case. In another similar case the red cells numbered 6,000,000 per c.m.m. and the hæmoglobin was 115 per cent. Yet this patient's blood was examined solely because the obvious pallor suggested that this ought to be done. The same type of case is not uncommon and most people must be familiar with examples of people who go through life quite satisfactorily in spite of a complexion that is the amazement of first acquaintances.

There is a second type of case in which the pallor is temporary and depends on nervous influences. One may often read that the hero or heroine stood as white as a sheet on the announcement of the unexpected visitor or the tragic news. This occurs in a less degree in everyday practice—it is not at all uncommon for a patient to become pale when the doctor enters the room. If it were not also far from uncommon for the said doctor to be beguiled into ordering iron there would have been little need to mention these cases. In chronic morphinism, in nephritis (although here there is often true anæmia), after residence in the tropics and in various other conditions of which tabes dorsalis is a common example there is also a false "anæmia," *i.e.*, a deceptive pallor.

On the other hand in true anæmia there is very often a yellowish tint, faint perhaps but quite enough to make the white pallor of false anæmias obvious by contrast. This yellowish tint is so common in anæmias that there is a certain danger—the writer has known of instances—of its confusion with the slighter degrees of jaundice.

Finally the intense pallor associated with some forms of cyanosis (see pages 292 and 298) is not to be considered an instance of anæmic pallor—it is spurious, an illusion produced by the absence of any of the characteristic red tint that one expects to find even in cases of cardiac or pulmonary cyanosis.

Pallor, then, is not an absolute criterion of anæmia nor does a good colour necessarily mean that it is absent. In neurotic persons pallor is commonly due to cutaneous vaso-constriction and not to anæmia.

Among the symptoms of anæmia to which little attention has been given is fever. Generally speaking anæmia per se does not seem to be associated clinically with fever but there are grounds for thinking that a distinct rise of temperature may be met with especially in hæmolytic anæmias which owns no other cause than blood destruction or metabolic disorder thereon consequent. This may be considerable and of some duration.

The general symptomatology of anæmia is of course largely that of whatever disease may happen to present in an individual case. It is proposed to deal here only with symptoms that are conveniently referable to the anæmia itself and these will be found to be largely those of oxygen starvation and of degeneration—especially vascular degeneration.

Nervous System.—Headache is common and is almost invariable in all severe cases. It is not infrequently accompanied by dizziness which may only be apparent on rising from a stooping position or on exertion. Both would appear to be in some way dependent on cerebral anæmia. This may be so marked a feature of the case that actual loss of consciousness occurs but less pronounced "fainting attacks" are more commonly met with.

Tiredness and weakness are complaints familiar to all and not infrequently form the chief subject of complaint when the patient first comes under observation. It may exceptionally be so intense that the patient considers herself paralysed or makes use of the word paralysis in describing symptoms.

At the same time it must be noted that an exactly opposite state of affairs is sometimes seen—a patient suffering from really severe anæmia says that he has been at work and has been able to accomplish the usual amount until a few days before he sought medical advice. This anomaly is not satisfactorily explained.

Subjective feelings of warmth, chill, numbness, etc., are not very common, but an increased susceptibility to cold is quite a common occurrence. This is not at all surprising since metabolism is less active.

Mental symptoms are more common than is generally recognised. If at all marked they are almost always of the confusional type. They are accompanied by either excitement or a more or less stuporose state. The excitement would seem to be especially frequent in acute cases, *i.e.*, in which the anæmia has developed acutely or undergone acute exacerbation. There is then both motor and mental excitement and the control of the patient may be difficult. There is often a low blood pressure at the time. On the other hand—typically toward the close of a severe anæmia—depression is apt to supervene and may mask the accompanying confusion which is more easily noted in excited cases. This depression is usually an affair of a few days but not very uncommonly may persist for a longer time and be recovered from. It is a bad sign in most cases heralding the death of the patient. A few cases have had to be removed to asylums. Mental symptoms are probably a sign of oxygen starvation (see also page 286 et seq). Short of what we may call mental symptoms a change in the personality of the patient is not uncommon—usually in the direction of increased irritability.

The occurrence of hæmorrhage may cause a great variety of nervous symptoms but these depend only indirectly on the anæmia and have been already mentioned when treating of other diseases.

Among less common affections of the nervous system are neuralgia, disturbances of speech, and the symptoms of combined sclerosis seen typically in Addisonian anæmia. The neuralgia in acute cases is commonly seen to affect the cranial nerves and may be very intractable. Disturbance of speech is in the direction of aphasia but is a rare symptom in such circumstances that it can be ascribed to the anæmia alone and not to any co-existing condition.

The nervous symptoms of Addisonian anæmia are more fully described on page 239 but a word is necessary in regard to their occurrence in secondary anæmias. That they depend entirely on the anæmia is not certain and the suggestion that this is so seems to be somewhat falsified by their presence in few cases only of a very common disease. The writer has never seen symptoms of combined sclerosis in a case of symptomatic anæmia but certain alterations have been found in the brain and cord of patients dead of post-hæmorrhagic anæmia. These degenerations would appear to have been capable of producing symptoms during life. We must therefore admit the possibility of the nervous syndrome associated with Addisonian anæmia being also met with in symptomatic anæmias without weakening the assumption that their more frequent occurrence in the former disease may be evidence of a toxin elaborated in that variety of anæmia.

Special Senses.—Optic neuritis is not infrequently reported as occurring in anæmia but the grounds for assuming that it is due to the anæmia alone are not quite satisfactory. Sudden blindness passing off early may occur in acute post-hæmorrhagic anæmia and this is perhaps explicable on the grounds of sudden alteration in the intra-ocular blood pressure. If these latter be long continued a more permanent condition may result. Fatty degeneration of the retinal vessels is a result of chronic anæmia and not very infrequently leads to hæmorrhages from the retinal vessels which may disturb the sight. Optic neuritis or papillitis is more often met with in chlorosis (see page 312) than in any other variety of anæmia and the possibility of thrombosis of the cerebral sinuses as an underlying cause should be borne in mind.

Pallor of the discs, narrowing of the vessels and other slight changes in the fundus are not infrequent and are of little significance.

Circulatory System.—The heart is affected by fatty degeneration of some degree in the great majority of cases of anæmia and this should always be borne in mind and treatment directed accordingly. This degeneration may apparently come on much more speedily than one would at first expect. We must remember that the heart alone is never able to rest. All the other organs can make up for the deficient supply of oxygen by limiting their activity; this the heart cannot do. Hence it degenerates more easily as a result of anæmia.

In acute cases there is danger of the patient imperilling life itself by too sudden movement, especially when the often quick return to a feeling of good health is by no means in accordance with the degree of anæmia actually present or of change in the heart. A similar condition is, of course, seen in diphtheria and other infective disorders.

After the blood has returned to normal the heart may still have failed to regain full functional efficiency and this again may be a cause of danger to the patient from too sudden exertion.

In chronic anæmias the degeneration of the heart is more generally recognised and is a very serious factor as is shewn by the frequency with which death is due to heart failure accompanied by œdema, etc.

Clinically the state of the heart is often reflected by slight enlargement and by repeated irregularities of the pulse. The regularity of the pulse or otherwise is an important factor when we come to consider whether an anæmic patient should be allowed up or not and in the consideration of similar problems.

Hæmic murmurs are more fully discussed under chlorosis (see page 308). They are very commonly present in symptomatic anæmias.

Thrombosis is rare and it may be doubted whether it ever depends solely on the anæmia. In any case this is not a hypothesis to be depended upon for clinical guidance.

There is a tendency to hæmorrhages but this is seldom marked in any but the graver cases. It presumably depends upon the fatty degeneration of the vessels already referred to. Purpura and epistaxis are relatively common manifestations of this tendency and menorrhagia and metrorrhagia also occur. Hæmorrhage from the gums is almost confined to the last stages of fatal cases.

Besides the tendency to hæmorrhages there is often a well-marked "hæmophilic" tendency. This is often shewn by the excessive and prolonged hæmorrhage which occurs after a small prick in the ear. It is probably due to the fact that an anæmic blood although not necessarily poor in fibrin lacks the other essential of a good clot, viz., corpuscles. The clot in consequence fails to plug the mouths of bleeding vessels and the hæmorrhage continues. Whether there are other tendencies at work cannot be said with any certainty—possibly there is a deficiency in the serum.

The Marrow.—It is here that the differences between the various types of secondary anæmia are most pronounced. In fact the marrow—as the organ responsible for determining the condition of the blood—must always be of primary importance in the consideration of anæmia.

In the secondary anæmias it is either in a state of atrophy or hypertrophy.

If in a condition of atrophy, this is nevertheless seldom absolute; there are always small islands of repair although they are not numerous enough to affect the general condition or the clinical picture.

Furthermore the atrophy may take different forms. There may be a general recession of the marrow from the areas that it formerly occupied, its place being taken by fat. In the remaining red marrow, however, the condition may be nearly normal but more usually shows an increase of fat and a diminution in red cells.

In other forms especially in cases of chronic sepsis and prolonged anæmia there is a considerable amount of gelatinous change. This is a metamorphosis of fat cells and not of red or white marrow cells so that it must be regarded as merely an addition to the condition of atrophy last described. This it certainly is clinically, *i.e.*, it has no signs peculiar to itself except such as can be seen after death.

The other variety of atrophy is more artificial and consists in the diminution of blood-cell-forming areas by encroachment of new growths. The remaining functional marrow may here be normally active but is often affected by the tumour growth in a secondary manner, *i.e.*, by lowering of the general vitality.

The conditions in which atrophic marrow is found have already been mentioned (page 195) but it may again be insisted that to this complexion do all secondary anæmias come at last—or the great majority of them.

In atrophic anæmias the marrow puts forth poor cells, poor in hæmoglobin, size, etc. These are more fully dealt with later. The output of white cells is usually also reduced.

In hæmolytic anæmias the marrow is usually in a state of activity, at least at first, for there is no more powerful inciter of blood formation than blood destruction. This activity is shown in the usual way by an increase of the red marrow at the expense of the yellow. There is also an increase in white-cell formation although there may be no ostensible cause for this such as sepsis. If the hæmolysis be acute the type of cell put forth differs notably from that seen in other types of anæmia. The cells are not poor in hæmoglobin nor in size but on the contrary approach the "pernicious" type and are not infrequently identical with it. This type of cell is the rule in hæmolytic anæmias but the exception in atrophic and post-hæmorrhagic cases.

In post-hæmorrhagic anæmia the marrow is also in a state of activity but is not usually of the dark almost purple colour seen in hæmolytic anæmias. It encroaches similarly on the yellow or fatty marrow. There is an increase of white-cell formation.

It should be mentioned that the term encroachment on the yellow marrow or similar terms are not to be taken too literally. It is true that the new growth of cell-forming marrow takes place chiefly at the margin of that previously active but it consists not in a true spread but in an hypertrophy of minute preexisting cell areas in the yellow marrow. The latter are always present.

The bone which contains and limits the marrow activity does not escape alteration when the marrow is in an altered state of activity. In the atrophic form there may be a distinct thickening of the trabeculæ and in other forms a similar absorption of them. In the latter there may be thinning of the shafts of the bones but this is never sufficient to cause fractures. The changes may in favourable circumstances be seen with the X-rays.

The Blood.—Here again it is necessary to distinguish three types but these are not nearly so definite as the necessity for separating them would seem to indicate.

In atrophic anæmia there is diminution of the red cells of varying extent, not commonly falling below 1,000,000 per c.m.m. but not exempt from such happenings. The hæmoglobin is lower in proportion than the red cells and the colour index is therefore low. The red cells may have less than half the proper amount of hæmoglobin. On the whole they tend to be rather smaller than normal but of course there are always a few larger than normal. They exhibit polychromasia and stippling in various degrees—not always in the same degree since one change may be present without the other. In a few conditions these colour changes are very pronounced and of these lead poisoning is a good example. Poikilocytosis is not a marked feature although the poor quality of the cells may lead to considerable distortion in spread films. When this is the case the cells in the counting chamber, however, will show much less change. Nucleated red cells are found in severe cases—they are normoblasts and show marked polychromatophilia and raggedness of the cytoplasm. Signs of division in the nucleated cells are rare in this form of anæmia except in the event of a blood crisis, which is rare.

There is often a leucocytosis but this is due to the fact that the cause of the anæmia is usually a cause also of leucocytosis, *e.g.*, sepsis and cancer. The author has met with as many as 70,000 white cells (in a case of very chronic pyæmia) but although much higher counts have been recorded this is still an unusually high figure. It may be mentioned as a matter of interest but not commonly of importance that especially high counts are likely to be met with and have been recorded in suppuration of the thoracic duct—the pus being poured directly into the circulation. In the more chronic cases there is a leucopenia with relative excess of the lymphocytes which, however, are not absolutely increased.

In hæmolytic anæmias the blood is rather different, as one would expect, seeing that an hypertrophic instead of an atrophic condition of the marrow is reflected in the blood stream. The red cells are diminished in varying degrees and there is nothing pathognomonic about the degree of anæmia. In acute cases such as may follow the indigestion of blood poisons or exposure to their fumes the primary fall may be as great as the fall which takes place in Addisonian anæmia, *i.e.*, to the neighbourhood of 500,000 per c.m.m. In such a case the red cells may show actual fragmentation and any process of repair is commonly absent for one or two days. Then there is a shower of nucleated red cells and the blood quickly assumes all the characteristics of the "pernicious" type. There are megalocytes, microcytes, a high colour index, and plentiful variations in shape and staining reaction. At the same time there is a leucocytosis and this may reach as high as 50,000 per c.m.m. As the patient recovers the blood slowly returns to normal.

If on the other hand a patient is exposed to chronic poisoning by some hæmolytic agent the "pernicious" type of blood may fail to develop. This type of blood is of occasional occurrence in all varieties of anæmia. It has been supposed to be especially prevalent in the anæmia associated with the presence of the fish tape worm or bothriocephalus but this is not a fact, although it does happen that it has been described in many cases of that disease—as an example of the fact that "pernicious anæmia" owns a great variety of causes. (For the "pernicious" type of blood picture see also page 243.)

In post-hæmorrhagic anæmias there is at first no change in the blood. Practically as soon as the blood volume is restored to the normal the first changes are noted. There are often nucleated red cells present in small numbers and these are normoblasts. The ordinary red cells are poor in hæmoglobin and sometimes seem also poor in size. There is usually a well-marked polychromatophilia and this is such that some of the cells seem to have no affinity for the red dyes at all.

Recovery from the anæmia is always marked by a return to the normal on the part of the red cells occurring some time before the hæmoglobin does the same. It must be remembered that the excessive polychromatophilia seen in some of the red cells in this condition is merely evidence of their hurried manufacture and that it may also be seen when hurried manufacture is necessitated by some other circumstances than hæmorrhage, *e.g.*, in association with a blood crisis dependent solely upon cardiac failure.

There is a leucocytosis of 10–30,000 in post-hæmorrhagic anæmia but this falls as convalescence progresses. The polymorphs predominate.

Finally it may be noted that diagnosis from a blood count alone is a radically unsound way of approaching the study of an individual case of anæmia and the distinctions here laid down as between the types of blood in the several varieties of anæmia must be taken as merely indications of the average findings and not as necessarily applicable in every case.

Spleen.—Generally speaking this is not affected in the secondary anæmias, *i.e.*, as part of the anæmic process as distinct from the disease causing the anæmia. Of course in such a disease as ulcerative endocarditis the anæmia is often very severe and the spleen also very large but in this case the splenomegaly is a symptom of the endocarditis and not of the anæmia. These cases are not very infrequently confused with the primary splenic anæmia of adults and should there be an absence of any definite cardiac signs the confusion is almost unavoidable.

In hæmolytic anæmias, especially if the onset has been sudden, there may be enlargement of the spleen and also tenderness on percussion over the splenic area. The enlargement is never so great as that met with in splenic anæmia proper, in leukæmia, erythræmia, etc.

Microscopically there may be evidence of increased blood destruction in the shape of exceptional activity of the endothelial cells, presence of large amounts of pigment and partially destroyed red cells.

Lymph Glands.—These are not affected. The hæmolymph glands may be enlarged if for any reason the spleen has not been able to deal with the necessity for disposing of immature corpuscles or red cells destroyed in the circulation by some blood poison.

Osseous System.—This is unaffected. Only in the hæmolytic anæmias of the acutest sort may there be tenderness on percussion of the bones.

Respiratory System.—This system does not demand very particular notice and is as a rule free from manifestations of anæmia with the exception of some degree of dyspnœa. This itself is properly referred not to the lungs but to the heart and the blood condition. It varies a great deal in intensity but in even very severe anæmia the patient does not show respiratory distress while at rest. There will, however, almost invariably be a complaint of breathlessness on exertion, *e.g.*, on going upstairs or uphill—in severe cases on sitting up in bed.

Œdema of the lungs occurs as part of the general tendency to œdema in the later stages. There does not seem to be an especial predisposition to lung troubles of a septic nature although one might expect this to be the case.

In the presence of obvious lung trouble of slight extent it may be difficult to say of it whether it is primary or secondary. This is particularly the case in tuberculosis. The safest rule is to regard nothing as due to the anæmia alone unless other factors can be definitely excluded.

Alimentary System.—In dealing with this system the difficulty above referred to is often one of real importance. Gastric and intestinal symptoms are very often met with in association with anæmia. They are potent primary factors and frequent secondary expressions of anæmia. When the gastrointestinal system is examined by special methods there is usually no abnormality to be discovered, *e.g.*, the amount of hydrochloric acid is normal or even increased, the motor power does not seem to be deficient, etc.

The appetite is very various, in a few cases there is a voracious appetite which suggests that the food taken is not assimilated. In such cases the consequent overloading of the stomach is a distinct disadvantage to the patient and should be avoided by giving frequent meals at smaller intervals than is usual. Peptonised food may also be given and bitter or other appetising substances avoided. In other cases the appetite is normal and the absorption of food apparently normal also.

In perhaps the majority of cases there is some failure of appetite at least at first but perversions of appetite are less common than in chlorosis, in fact, distinctly rare. The appetite is likely to improve of its own accord as the anæmia disappears but there is no harm in giving a tonic in early stages, *e.g.*, gentian, if it seems indicated.

The stomach, as already mentioned, is seldom abnormal except for pallor of the mucous membranes and it is probable that when pain is referred to this organ there is often a large psychic factor present. At the same time it is an undoubted fact that vomiting is a fairly common feature of anæmia and one for which the psychic element is not a very satisfactory explanation.

There is one particular type of vomiting which has been described as "anæmic vomiting" and which is certainly an important clinical feature of many secondary anæmias.

In this type the vomiting and pain in the epigastrium may be so severe as to seem to warrant operation. There is, however, an absence of more than rather trivial constitutional symptoms and there is often infra-mammary pain or tenderness as well as that in the epigastrium. The vomiting may occur whenever food is introduced into the stomach but a careful questioning will probably elicit the fact that severe paroxysms also occur independently of the taking of food but in direct relation to undue exertion. The heart is found enlarged and this is the real cause of the vomiting and determines its onset after exercise.

The obvious treatment is rest in bed and small doses of Liq. Arsenicalis are recommended (3 minims t.d.s.). There is no need to restrict the diet, in fact it should be as full as is possible in view of the fact that a dilated heart case does not as a rule deal well with large quantities of food at one time. It is also necessary to tell the patient—probably neurotic—that there is no organic disease and generally to administer advice as well as nourishment. Bismuth is of no value in this class of case but in the chronic forms of indigestion may be useful.

Some degree of dilatation of the stomach is not very uncommon and flatulence is then a frequent complaint. It is then often well to diminish the intake of fluid at meal times.

Hæmorrhage from the stomach is a terminal symptom when it depends solely on the anæmia. Little can be done in the way of treatment when terminal hæmorrhages have shewn themselves.

Constipation would not appear to be a symptom of anæmia per se although not infrequently present. Diarrhœa on the other hand is more common but is, even so, less often seen in the secondary anæmias than in the generalised diseases of the blood-forming organs.

It yields readily to treatment.

The Liver.—This is not affected except by fatty changes in advanced cases. In the hæmolytic cases it may give a well marked iron reaction. Ascites is usually a terminal feature if present at all and depends not directly on the anæmia, but on heart failure.

Urogenital System.—This system is not usually seriously affected in anæmia but certain points require mention. Albuminuria is not uncommon and does not make the prognosis any more grave than if it had been absent. Blood is seen in the urine in some cases but this is on a par with hæmorrhage in other parts of the body, *i.e.*, is a terminal symptom as a rule. In the hæmolytic anæmias the urine is often dark in colour and in the absence of jaundice, constipation, or concentration of the urine as by fever is a tolerably good sign of blood destruction since there is then presumptive evidence of increased excretion of pigments and these are derived from the blood, *i.e.*, from the hæmoglobin. The fact that the urine is light in colour does not, however, exclude blood destruction since the pigments resulting from it are primarily excreted in the bile and those which appear in the urine are only a small proportion re-absorbed from the intestine. If there is diarrhœa or for any other reason diminished opportunity for re-absorption the colour of the urine may be normal. Moreover many of the pigments resulting from the destruction of hæmoglobin are capable of existing in forms which have a very small colour intensity and so may not be apparent without special tests although present in increased amount. Unfortunately these tests require a laboratory for their proper performance.

In severe cases of anæmia the kidneys may be damaged by fatty changes and then fatty casts may be found in the urine.

Where there has been considerable destruction of blood in the vessels of the body, as in paroxysmal hæmoglobinuria, black water fever, etc., the onset of suppression of urine may be very sudden and should always be guarded against by a copious administration of fluid, subcutaneously if necessary.

In women menorrhagia or even metrorrhagia is not very uncommon, but it is well to be very chary of accepting either as a symptom of anæmia rather than as the cause. They may of course occur in severe cases as a part of a general "hæmorrhagic diathesis." This latter term is one rather frequently used but should be employed only when it is understood to imply a strictly acquired (as against congenital) tendency to bleed. Such a tendency develops in cases of anæmia when the fatty changes in the vessels have progressed far enough whether these be due to the anæmia or to some toxin, *i.e.*, that absorbed from septic gums.

Anæmia is a potent cause of the various mishaps which may occur to a pregnant woman and may result in miscarriage or in the production of a feeble child—perhaps with no potentiality of ever fully recovering the health lost in utero or never acquired. If the mother at the time of pregnancy has a small supply of iron in her body and needs most of that for her own nourishment there is every likelihood of the child being born with a poor supply of iron. As the natural food of the infant does not contain iron nature endeavours to supply it with enough iron already stored in the liver at birth to carry it through the first months of extra-uterine life. If this has been impossible the child naturally suffers. It is therefore important to see that pregnant women who show any tendency to anæmia have that tendency corrected.

Pregnancy is usually cited as one of the causes of what is called "pernicious anæmia." It is impossible to say what exactly the term may mean except that it undoubtedly includes the specific disease described here as Addisonian anæmia. It does not appear that this disease is particularly apt to appear in pregnant women so that the so-called "pernicious anæmia" of pregnancy is probably only a severe secondary anæmia. For this there are many obvious and sufficient reasons, for pregnancy is often associated with such sequelæ as profuse bleeding, prolonged lactation, and various exhausting factors.

The Skin.—The point about the skin to which attention is usually directed is its pallor. This has already been referred to (see page 197), but it may be mentioned here that pallor without any yellow tinge at all is almost certainly either vasomotor in origin or else indicative of post-hæmorrhagic anæmia. In other conditions and very often even in post-hæmorrhagic anæmia there is a yellow tint. This is probably due to absorption of the products of blood destruction and occurs especially in those diseases such as Addisonian anæmia and cholæmia in which this destruction is most marked. It also occurs naturally enough when, owing to hasty new formation and hence presence in the blood of immature corpuscles, there is blood destruction in any variety of anæmia. It may be very marked during the absorption of altered blood from the bowel but this is not regularly the case.

Diagnosis.—This depends in the first place on the presence of pallor and appreciation of its significance. Pallor is a symptom very commonly misinterpreted. It does not necessarily connote any deficiency in the blood and may be due to a variety of other causes. These all have in common some affection of the vessels. Usually there is some constriction of the vessels driving the blood from the more exposed parts, *i.e.*, those parts which we usually look to to reveal any signs of anæmia. In neurotic persons it is very common indeed to find a considerable degree of pallor—which is heightened when the doctor calls—dependent solely on constriction of the peripheral vessels. The writer has frequently seen iron prescribed for such persons and has had the opportunity in many cases of examining the blood which was often actually above normal in amount. Those who take morphia exhibit a similar pallor in many cases and so do those who have resided abroad. Except in the latter case where there may be some effects of the sun a yellowish tinge is very good evidence of the existence of anæmia—even better than a white one provided there is no jaundice. The respective yellow tinges ought not to be confused.

The existence of pallor is best seen in the conjunctivæ, lips and beds of the finger nails.

An examination of the blood will verify the diagnosis as far as the existence of anæmia is concerned. The variety of anæmia can seldom be elucidated except by the history although the blood changes already mentioned are of value in this connection. It must be mentioned that loss of blood from hæmorrhoids and from the vagina is frequently concealed from the physician unless he makes specific enquiry so that this should not be omitted.

Treatment.—This is very simple—it follows well recognised lines and in no disorder can we be more certain that nature will assist if given a fair chance. At the same time it may be well to mention that anæmia ought to be treated and that treatment of concurrent disease may suffice but is not to be recommended as the sole remedial effort.

The cardinal principles in the treatment of anæmia are rest, good hygiene and removal of the cause. The last is less likely to be overlooked and is therefore put in that position. The former two are sometimes hard to enforce or for the patient to obtain. Rest means actual rest in bed in severe cases and the minimum of effort in all others. Good hygiene includes especially good food—good air and sunlight are also very important. The latter are often omitted in the plan of treatment. This is a great mistake. A patient, even if the red cells are below 1,000,000 per c.m.m., should if possible be in the open air and as far as possible in full sunlight all day. This is of more value than much arsenic. Good food is not sufficient if it is not properly assimilated. Assimilation must therefore be assisted according to the degree of anæmia. In severe cases peptonised and predigested foods should be given. In others it may be sufficient to give only the most nourishing foods. It is better to give a little frequently than a great deal at one time. Tonics are very useful inasmuch as they stimulate the intestinal tract and help to restore the muscular tone.

Removal of the cause may entail a great variety of measures. No matter what has been done the cause cannot be said to have been properly removed if there remains a single septic focus in the body—whether in the mouth, the intestine or the pelvic organs. It is happily becoming more generally realised that pyorrhœa is a disease to be treated with care and respect but it may be noted that a tooth plate which is seldom or never removed is as bad as a tooth bathed in pus. Yet such plates are not infrequently met with and some few dentists, of the sort who carry out bridging and crowning operations, even affix plates which are not intended to be removed. The recognition of this fact is of the greatest possible importance if a cure is to be attained.

SPLENIC ANÆMIA OF INFANTS

Synonyms.—Von Jaksch's Anæmia. Pseudo-leukæmia infantum.

Definition.—A symptom complex met with—often in association with infective disorders—in infancy and usually associated with massive enlargement of the spleen and certain characteristic blood changes.

Nature.—This is probably in nearly every case an infective disorder but its tendency to affect twins and its frequent association with rickets suggest that infection alone cannot produce the full syndrome. There would seem also to be some predisposing factor of which we are ignorant.

General Pathology.—Of this we know almost nothing. Both the blood picture during life and the marrow after death seem to suggest excessive activity of the blood-forming tissues. Unfortunately we cannot say that the extent of marrow area is enlarged because at the age at which this disease is encountered the whole of the marrow is normally active tissue and fatty marrow only takes its place later.

Granted this overactivity we are faced with much the same difficulties as in Addisonian anæmia. The blood condition may be due to excessive blood destruction or to primary "degeneration" of the marrow. There is no evidence in favour of the latter view except the resemblance of the blood condition to that met with in leukæmia in adults. Nor should we expect to meet with any change of a degenerative nature in infants, moreover this is not a fatal disease but one in which the prognosis is good.

In favour of the blood destruction being a primary factor we have similarly practically no evidence. The signs of hæmolysis are usually to be met with in the urine but the urine of infants is difficult to collect and this renders continued observation impossible. It is true that the fæces also show excess of the products of blood destruction but we are met with similar difficulties here also. The almost constant association with some intestinal infective disorder may provide the source of the blood destruction and it is certainly a fact that when the intestinal condition improves the blood usually improves also.

As is usual when splenomegaly is considered we have to admit that we are completely ignorant as to the true part which the spleen plays in this disease.

Etiology.—Rickets and syphilis have often been incriminated in this connection. In the latter case there is no evidence whatever except the difficulty experienced by some people in suggesting any other cause for obscure diseases. As to rickets one can only say that it is usually present but whether in a direct etiological relation or not it is impossible to say. It is the writer's view that rickets may predispose to intestinal infection and thus produce splenic anæmia or that the real predisposing cause may antedate both the rickets and the anæmia and stand in an etiological relation to both.

Age and Sex.—The sexes are about equally affected. The age at which the disease usually appears is seldom so early as six months or so late as two years. The average case when first seen is just over a year old.

Onset.—This is always gradual and increasing pallor and fretfulness are the first signs. Green diarrhœa is commonly present.

General Symptoms.—These are such as one expects in most illnesses of infancy and do not present any very marked characteristics peculiar to the disease beyond the splenomegaly and anæmia.

Fever is usually present and is very variable in character. Fig. 27 shows part of the chart of a case in which the extreme irregularity is obvious. This was an interesting case inasmuch as the rise of temperature on the 12th day shewn in the chart was taken by two or three medical men to be a terminal rise and to portend an almost immediate fatal result. As soon, however, as treatment by withholding food and giving rectal salines was commenced the child improved and made an uninterrupted recovery.

The Blood.—The red cells are reduced in number to below a million in extreme cases. This extent of reduction is more often met with than one would expect but is not incompatible with recovery. The red cells show all possible variations in size and shape—in an extreme case the blood picture is precisely similar, as regards the red cells, to that of Addisonian anæmia. The nucleated red cells which are always present show every variety of nucleus including the most beautiful mitotic figures in many cases. Fig. 42 shows a mitosis in a case of congenital heart disease but this might as well have come from a case of splenic anæmia of infants. Such figures are not found in other conditions than those mentioned except only in leukæmia of the myeloid type, or, if at all, very rarely indeed. The hæmoglobin index varies extremely.

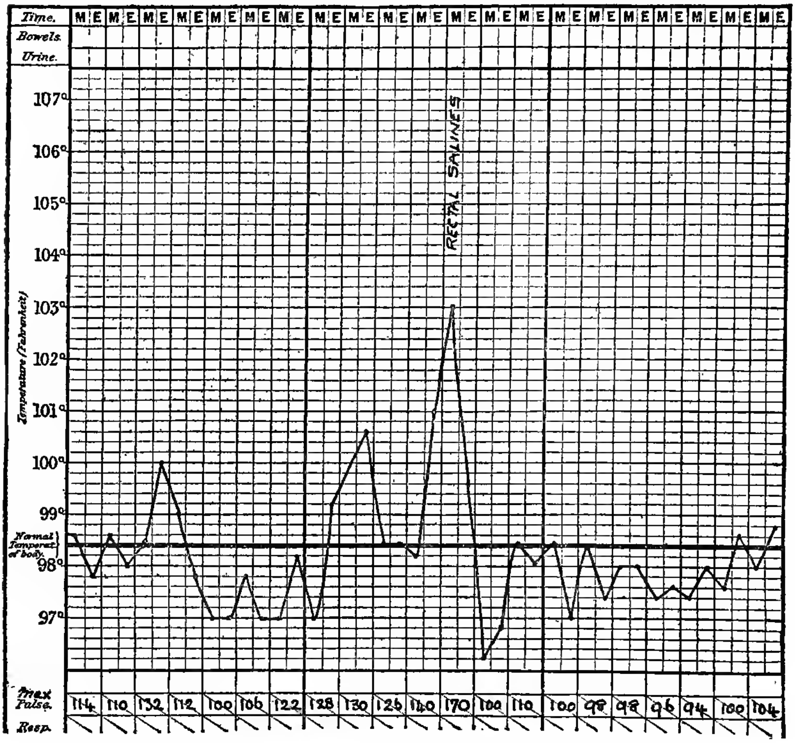


FIG. 31.—Three weeks' temperature chart of a severe case of splenic anæmia in an infant of twelve months. The highest daily temperature was often noted in the morning—a peculiarity of the case and not of the disease. The administration of rectal salines produced immediate improvement although the child had previously appeared on the point of dying. The case terminated in complete recovery.

The white cells are increased in number and in variety. As a rule they do not reach above 20–30,000 per c.m.m.

Often they are very much less. Polymorphonuclears are in a majority but compared with the adult counts are reduced, *i.e.*, they may be about 40–60 per cent. The lymphocytes as is usual in infancy are more numerous than in the adult. In this disease there is commonly an increase of both polymorphs and lymphocytes, *i.e.*, a mixed leucocytosis. This is seen also in pertussis and rarely in other diseases, especially in infancy, but must be regarded as a rarity. Myelocytes are constantly present and these are of a more primitive type than is usual in the leucocytosis of adult infective diseases. They are commonly pre-myelocytes, *i.e.*, at a stage at which the protoplasm stains very deeply with the blue basic dyes and has no granules. In an adult changes in the blood of this sort would probably justify a diagnosis of leukæmia; in a child one has always to be prepared for a quick reversion to the primitive type of blood formation under comparatively small stimulation.

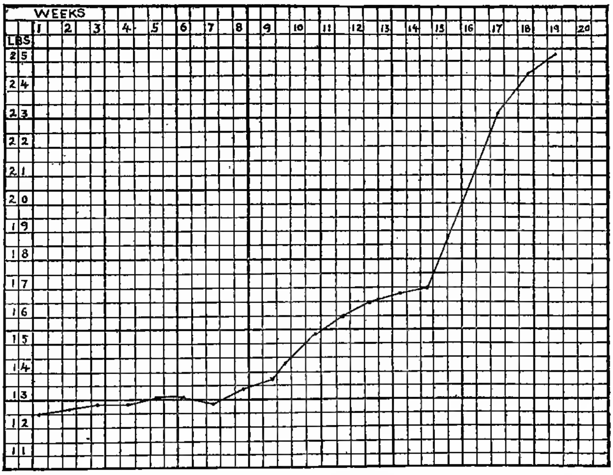


FIG. 32.—Chart of the weight in a case of splenic anæmia of infants, showing the absence of any increase in the early period due to decrease in size of the spleen. Clinically there was steady and progressive improvement. The sharp rise about the fifteenth week is due to transfer to the country.

Spleen.—This is enlarged to a variable extent and the enlargement is always of the "massive" type, *i.e.*, it is not only big but it feels peculiarly firm and homogeneous. On section it does not show any signs other than those of simple hypertrophy which can be called typical of the disease.

Evidence of increased blood destruction is always present but in any given section the amount of blood destruction may appear normal—the total increase is due to the total increase in size of the spleen.

Peri-splenitis seems to be rare; it is certainly not so frequent as it is in the various adult types of splenomegaly nor are signs of it commonly found post mortem. In the same way the infant does not seem to suffer from acute attacks of pain (except such as are due to colic) although a dull ache is probably present.

The size of the spleen diminishes as the anæmia improves. This is a point to be borne in mind in all its bearings. One not infrequently finds that a child although apparently making headway is losing weight or gaining very little. This is due to the diminution in size and therefore in weight of the spleen. In the same way the influence of œdema in producing increase of weight has to be remembered in many diseases.

Lymphatic System.—The lymphatic glands are not enlarged.

Liver.—This may appear enlarged but it is often difficult to estimate exactly how large the liver ought to be in an emaciated child—and most of these are emaciated.

Course.—Without treatment the course progresses to a fatal conclusion. There seems to be little power in nature unaided to deal with this disease when it is once established. Perhaps one ought rather to say that the establishment of this syndrome is a sign that nature has given it up and it is time man had a try at cure.

Fortunately man is very often able to restore nature's discarded plaything to vigorous health. No general prognosis can be given but in no disease is there a necessity for more continuous attention and in few so good a prospect of reward. The prognosis does not depend on the blood condition, which is merely an index of the extent to which the disorder has progressed, but on the general condition of the patient and the presence of removable causes. The duration varies—in a fatal case death may occur within six weeks to three months of the onset of the disease. In a case which is improving the period to complete cure will probably be longer—up to a year or more—but the signs of improvement justifying a hopeful prognosis will appear within a week or two of the institution of proper treatment.

Complications.—These include all the ills of infancy, especially rickets and gastro-intestinal disorders, although broncho-pneumonia, etc., are also met with. In one case the writer has observed some improvement coincident with the development of a crop of abscesses about the buttocks but the encouragement of abscesses is not advocated as a means of cure. The occurrence is of interest in view of the action of sepsis in leukæmia (see page 104).

Treatment.—There is no specific treatment and very little directed to the blood condition—which is, after all, an unimportant feature of the disease from the clinician's point of view except in so far as it affords an index of the result of treatment. Care should be taken that there is enough iron available for the needs of the body but this only necessitates a minimal dose of whatever iron preparation is best compatible with the other drugs which the necessities of individual cases may require.

Grey powder is often very useful but this is true of a great number of children's ailments. Castor oil is better.

On the whole there can be no sort of doubt that the chief indication in treatment is to supply enough fluid to the body and to cleanse the intestinal tract. It is impossible here to detail the various measures which may be adopted for the latter purpose but certainly entire abstention from food for a day or two, at intervals if necessary, combined with rectal or subcutaneous salines is very efficacious. It is not pleasant for the child and to soothe the mother it is often necessary to say that albumen water may be given with some polite fiction as to the utter impossibility of the child assimilating anything else. Later the hundred and one questions of practical dietetics in infancy will obtrude themselves. The writer, although reluctant to mention proprietary articles, feels bound to mention that Virol often seems to be of the greatest value when nothing else of a like nature is efficacious.

Diagnosis.—If a child has a large spleen and is anæmic and there is no apparent reason for either condition that child has splenic anæmia of infancy, *i.e.*, the essential points of the syndrome are present. The blood examination will exclude leukæmia which is of course rare at this age. Myelæmia in which the spleen is more likely to be enlarged is especially rare.

If, however, the child is above the age of three years as a maximum when the disease shows itself it may be possible to assign the syndrome to a place alongside that occupied by the splenic anæmia of adults. The disease here dealt with is essentially a disease of infancy. It is possible that one may pass into the other and such cases have been recorded but the criteria of such cases on which a definite classification can be based are of so general a nature that a relation between the two diseases is not to be too readily assumed. Further, the number of such cases is extremely small.

SENILE ANÆMIA

Cases of this syndrome have not been described in England or America and it is very doubtful how far it can be considered a definite clinical entity.

It is related to splenic anæmia of adults but has also relationships with Addisonian anæmia. There is usually high temperature and development of subcutaneous hæmorrhages before death. At autopsy the marrow is atrophied.

The disease is met with in old men—about the age of 60.

There is marked splenomegaly and progressive anæmia and leucopenia and the colour index is sometimes above normal.

CHAPTER XI

CHOLÆMIA

Synonyms.—Acholuric jaundice, congenital or familial acholuric jaundice, hæmolytic jaundice. (Ictere hemolytique.)

Definition.—This name is applied to a condition characterised by jaundice, splenomegaly and a typical condition of the blood. It may be congenital or acquired and familial as well as sporadic cases are met with.

Nature.—This is not at present sufficiently elucidated to make a dogmatic statement possible—the matter is dealt with under General Pathology.

General Pathology.—Unfortunately we never see the commencement of this disease—it is either of very slow onset or congenital. We do, however, see the onset of somewhat allied conditions, *i.e.*, poisoning by filix mas, etc.

In such conditions there is a sudden onset of jaundice soon after taking the drug, this is followed by anæmia which may be of a month's duration and is accompanied by changes in the blood suggestive of actual destruction of the red cells in the vessels.

The sequence here would appear to be sufficiently plain—poison producing immediate destruction of the red cells and this in turn producing jaundice by overworking the liver (the organ responsible for eliminating the products of hæmoglobin destruction) and anæmia which lasts until the blood can be restored to normal state.

In cholæmia we find the same procession of events during the acuter exacerbations of the disease, viz., excessive hæmolysis, jaundice and anæmia. But there are in addition two factors on which so much stress has been laid that some mention of their place in the pathology of the disease is necessary; these are splenomegaly and increased fragility of the red cells. These may be considered separately.

What part does enlargement of the spleen play? It is usually extreme and only in the rarest cases absent. Probably these cases can be dismissed as accidental clinical pictures deviating from the usual type in virtue of the fact some other hæmolytic organ (*e.g.*, hæmolymph glands or even bone marrow) is taking that share in the disease which is more often taken by the spleen.

There remains then the fact that a large hæmolytic organ is found in a state of excessive activity. So much would seem natural since we already know that there is excessive hæmolysis. But removal of this organ seems to cure the disease. How is this to be explained if the enlargment is merely a secondary factor depending on the excessive hæmolysis in the blood stream. We can only explain it by supposing that the spleen has a more intimate connection with the hæmolysis than that of a mere accessory after the fact. There is considerable experimental support for this view of the functions of the spleen. Thus it has been ascertained that poisons of the sort that destroy the red cells while in the circulation act much less powerfully if the spleen has been removed before they are administered.

Thus we are forced to consider that the spleen has a twofold part in the disease, viz., that of a mere remover of dead corpuscles and that of an accelerator to the posion which kills the corpuscles. The first probably accounts for its enlargement, the second for the fact that splenectomy effects a cure. It should be remarked that this is a clinical cure rather than an entire cessation of the pathological process and this is exactly what we might have deduced from the foregoing remarks on the duality of the splenic function.

The increased fragility of the red cells mentioned as a fact requiring comment is merely part of peculiar blood picture of this disease. It means that the red cells when placed in saline solutions of various strengths allow the escape of their hæmoglobin in solutions sufficiently strong to prevent this happening in the case of normal blood. The other features in the blood are mostly connected with the type of cell met with, *e.g.*, very many of the cells are different from the normal in size and many are "stippled," *i.e.*, appear to be covered with small black dots when stained with a double stain instead of appearing of a homogeneous red throughout.

This increased fragility has been supposed to be the basis of the disease to which all other manifestations can be referred but this view cannot be accepted without hesitation. It would leave us quite unable to explain the connection of splenomegaly with the disease for we know very well that the mere blood-destroying functions of the spleen—the scavenger part of its activities—are taken up by the hæmolymph glands and other organs when it is removed. When therefore we find after its removal that the fragility of the red cells remains but there is no hæmolysis we are forced to believe that this fragility is not sufficient to doom the red cells to death. Moreover this fragility or increased susceptibility to hæmolysis is tested with regard to salt solutions and these do not reproduce the normal factors in hæmolysis or anything remotely like them.

We might suggest then that the pathology of the disease is somewhat as follows. The congenital cases are due to the elaboration of some substance owing to a defect of metabolism which is produced in the acquired cases under the more direct influence of syphilitic or other toxins.

This substance, acting through the spleen, produces increased fragility of the red cells or, when more potent, actual destruction of these cells. This in turn gives rise to jaundice and anæmia and also to an enlargement of the spleen due to its function as a scavenger on which increased calls are made by the increased blood destruction.

If this view be correct we should be able to treat the disease by intercepting the process at various points. A congenital disorder of metabolism we are not yet able to deal with but when this is produced by some recognisable toxin, such as that of syphilis, we ought to be able to remove this and so put a stop to the subsequent blood destruction, etc. This is actually the case, inunction of mercury or other suitable measures will produce a cure in many acquired cases of cholæmia. We should also be able to stop the process by removal of the spleen which would diminish or abolish the action of our hypothetical substance. This also we can do. Finally we ought to be able to employ some measures for rendering the red cells less liable to succumb to the hæmolytic agencies. It is only of recent years that the process of hæmolysis has been studied from this point of view and several drugs have been found which increase resistance to hæmolysis *in vitro*. Of these cholesterin in particular has been given to patients with the idea that it would increase resistance *in vivo* also. It would appear that this has been the case in some instances but the results are not very gratifying except from the purely theoretical point of view.

Allied Diseases.—There are very many diseases which may produce a clinical picture similar to that of cholæmia. Any familial form of splenomegaly associated with some jaundice will tend to cause confusion clinically but not as a rule pathologically. Clinical difficulties are dealt with under Diagnosis.

Icterus neonatorum and certain forms of jaundice very nearly allied but persisting for a longer period and having a familial incidence are undoubtedly related to cholæmia but so little is known about them that it is impossible to say more.

Again Addisonian anæmia is sometimes so closely simulated as to give rise to confusion and it must be admitted that all hæmolytic diseases present interesting analogies.

It is a noteworthy fact that removal of the spleen cures the disease, but does not necessarily do away with the fragility of the red cells. It would appear, therefore, that the spleen is necessary to the full establishment of the hæmolytic process but there is no evidence that it initiates the disorder.

Poisoning by filix mas must also be included as an allied disease. Another is the condition sometimes found associated with congenital occlusion of the bile ducts, either by intrauterine inflammation as some consider or by failure of development as others prefer to hold. In such a condition there may be a condition very similar to that found in cholæmia, viz., jaundice, anæmia, etc. The blood condition, however, is different and the fæces are acholic and these serve to differentiate the condition.

Etiology.—Heredity certainly predisposes to the disease and the question of heredity is very interesting.

There are some families in which the disease has been present in at least four generations. It has always been transmitted by an affected member. In some of these males only are affected, in others females only, in still others both sexes suffer.

In a few families the disease is not apparently hereditary but affects several members of one generation.

Sporadic congenital cases also occur.

In the families affected examination of apparently unaffected members has resulted in finding splenic enlargement with no jaundice, the blood changes and the jaundice with no splenomegaly, etc., in a word signs of the disease which would be very misleading and perhaps impossible to interpret if the family history were not known.

The acquired cases present the same clinical picture and of all factors syphilis seems one of the most potent in producing the disease. These cases will in all probability be separated off when we know more about them, at least for clinical purposes.

Acute attacks are predisposed to by any debilitating influence and especially by cold.

Age and Sex.—The acquired cases are not often met with in people below adult age but the hereditary form is apparent at birth or very soon after. Cases directly due to some known drug or poison may, of course, be met with at any age but are as a matter of fact usually met with after puberty—possibly on account of the more plastic nature of the means of resistance at the earlier ages which would tend to obscure the signs of blood destruction and perhaps prevent the development of jaundice.

Neither sex seems to be especially predisposed to attacks or to the congenital disease. It is usually transmitted by affected females but may be transmitted by males. It is not transmitted by unaffected persons.

Onset.—The first sign clinically is the jaundice. This may occur very soon after birth. It appears rather suddenly. The same appears to be true of the acquired cases but in these there is a period of ill health previous, as would indeed be expected. In the absence of any other clinical sign of the disease other than jaundice from which the onset of cholæmia can conveniently be dated we must say that the onset is sudden but at the same time it is to be borne in mind that there is no doubt a very slight blood destruction to begin with and this probably does not lead at once to jaundice.

General Symptomatology.—The remarkable point about these patients is that they enjoy such good health. Hawkins and Dudgeon's case of a policeman who was always fit for duty and had been in the force some years is a good illustration of this. He had a yellow complexion—which naturally had given rise to comment—and the other signs of the disease but had long ceased to worry about them. Another case was referred by a School Medical Officer for examination although the parents stated that the boy enjoyed the best of health as was indeed the case.

The general symptoms are weakness, anæmia, yellow colour, and splenomegaly; during the acuter attacks these are more marked. Later the weakness becomes more pronounced and hæmorrhage, usually epistaxis, occurs.

These symptoms may last unchanged for years and the patient may pass through the common fevers of childhood and even through operations without any difficulty.

Gall-stone colic is not an uncommon feature.

Fever.—This is not present as a rule except in the late stages and during acute attacks. It does not conform to any particular type and is of slight degree.

Nervous System and Special Senses.—These may be affected by hæmorrhages but these are rare. So far as the writer is aware hæmorrhage into the retina is the only class of hæmorrhage that affects the nervous system or special senses, but the occurrence of any other would not cause surprise.

Circulatory System.—There is nothing of note about the heart or vessels. In the acquired cases the vessels may show signs of syphilis and in any case there may be signs of this or other intercurrent disease.

The tendency to hæmorrhage is fairly well marked, but, contrary to the state of affairs commonly met with in splenic anæmia, the stomach and intestinal tract seem to be exceptionally free from them. Bleeding from the nose is the most frequent form of hæmorrhage, purpura has been noted.

Marrow.—This has been found to be in a state of great activity—so much could be legitimately deduced from the blood changes. It shows the type of cell that one would expect to find by a similar deduction—the blood seems to accurately reflect the marrow in this disease as it does in many others. The usual signs of blood destruction in the shape of pigment granules are present in the marrow.

Blood.—The blood changes have been fully worked out of recent years. The red cells may rarely be in excess of normal —presumably when the reaction of the marrow has got the better of the hæmolysis. More commonly there is some grade of anæmia and this is to be expected if the patient is sufficiently ill to come for treatment. The blood picture may resemble that of Addisonian anæmia especially in the late stages; certain features, namely the nucleated red cells, are almost constantly present. The degree of diminution in the case of a person congenitally affected who is temporarily suffering from symptoms may be expected to be from one to two millions.

The hæmoglobin is usually reduced relatively more than the red cells. The colour index is therefore below normal. This is not a constant feature of the disease and an index above unity is quite commonly met with although not in the majority of cases. A very favourite index is about 1.1—that is lower than that often met with in Addisonian anæmia but higher than unity. A very low index is not at all common, such for example as is met with in chlorosis and some cases of tuberculosis in which the index may fall to 0.3 or even lower.

The red cells show many changes. Their hæmoglobin content has been already discussed. In addition they show a well marked tendency to be abnormal in size. The majority are distinctly small and the average size is below normal but there are nearly always some that are very distinctly big. The latter are few. In a word there is greatly increased anisocytosis and general microcytosis. In addition there are usually present nucleated red cells. These are chiefly of the normoblast type and frequently show greatly contorted nuclei. These may show figures readily recognised as those of mitosis or anomalous varieties of division such as met with in blood crisis (see page 183). All the cells, or, rather, a considerable proportion of them show polychromasia to some extent and especially basophil stippling (see page 244). The latter with the tendency to a small size and the presence of nucleated cells make a very characteristic picture.

The red cells are also less resistant to hæmolysis by salt solution than are normal cells. The normal cell will not hæmolyse in 1.0 per cent. salt solution nor until the solution has been weakened down to 0.4 per cent. or 0.3 per cent. The cells in cholæmia will often hæmolyse unless the proportion of salt is 0.7 per cent. or 0.8 per cent., *i.e.*, there must be twice as much salt present to prevent hæmolysis in cholæmia as is necessary in normal persons. These figures present the average and are not to be taken as hard and fast limits. The technique is to immerse the red cells in salt solutions of varying strength but the method of hæmolysis varies so markedly from that which occurs normally and has, moreover, been so frequently demonstrated in cholæmia that it is becoming a matter on which further research is of small value. The question of hæmolysis by agents such as represent more nearly the normal process and of the resistance of cholæmia cells thereto is more important. It has been found similarly diminished in some cases.

The blood serum is of a yellow colour and this is due to the presence of bile pigments. Urobilin is not to be detected. Hæmoglobin is not as a rule found although it has been noted.

The white cells vary almost as much as the red but not so characteristically. The variations are such as can be attributed to the variations in the normal condition so frequently met with in children under the stress of anæmia and include the presence of myelocytes and a certain number of anomalous cells classified as large lymphocytes. These are the more likely to be present considering the active state of the marrow. The abnormal cells are usually few in number. The polymorphs—except in children—keep to about the normal 65–75 per cent., but the mast cells and eosinophils are not so stable and a small excess of one or the other or both would seem to be a fairly common feature.

The Spleen.—This is usually enlarged and the enlargement is usually massive. The remarks as to its size made under myelæmia, erythræmia and splenic anæmia apply as well to cholæmia—it may be very large and usually is but most other sizes are met with now and again.

Total absence of splenomegaly has been several times reported but there is no evidence as to whether the hæmolymph glands were enlarged in these cases. If this was the case the absence of any splenomegaly is more understandable.

The various troubles associated with enlarged spleens may be met with, especially peri-splenitis which is a fairly common symptom. Adhesions may result and subsequently give rise to trouble.

After death the spleen may show thickenings of the capsule and of the trabeculæ but otherwise shows nothing but signs of intense hæmolysis. The pulp is packed with red cells and the endothelial cells contain pigment and are actively phagocytic. Pigment is also found situated outside the cells.

Lymphatic System.—This is not affected, but the autopsies are few in number at present and it is probable that some enlargement and increased functional activity of the hæmolymph glands will subsequently be reported.

Osseous System.—This is not affected so far as the clinician can become aware. Again we may suggest that tenderness of the bones will be reported some day and also that X-rays will be found to show absorption of the cancellous tissue such as is found after death.

Respiratory System.—This is unaffected except for the dyspnœa, etc., which may be associated with the anæmia or the signs of previous or intercurrent disease.

Alimentary System.—This again is not affected except by the pressure results of the large spleen or inflammation around it. This remark, however, does not apply to the fæces which may be discoloured. This discolouration is very seldom due to absence of bile pigment although this seems to have been present in very occasional cases for a short time. As a rule the fæces are distinctly high coloured and it has been shown that they do as a matter of fact contain an excess of bile pigments. During the acute attacks this pigmentation may become very marked and the fæces may be almost of a green colour.

The constituents of the fæces other than those coming from the bile are normal.

Liver.—This is often slightly enlarged, especially during acute attacks and in acquired cases, and may then be tender. The enlargement is never extreme. Microscopically it does not show any evidence of fibrosis but there may be a considerable amount of pigment present—as is to be expected.

The gall bladder very often contains gall stones; no doubt this is a result of the increased inspissation of the bile during periods of acuter hæmolysis than usual. These may in turn give rise to cholangitis and gall-stone colic is not an infrequent symptom. The gall stones have been removed successfully in some cases but it would seem very probable that they would form again. However this would be a poor argument for refusing to give relief to a case in which gall-stone colic was very frequent.

Urogenital System.—The kidneys are normal except for the presence of pigment granules and some degree of fibrosis.

The genital system is normal and repeated pregnancies are possible in women affected with this disease.

The urine is not normal. It contains more than the usual amount of urobilin. A word is necessary as to the significance of this change. The blood pigments are normally so altered that they become the bile pigments. The reverse synthesis has not yet been possible beyond cavil but has been so nearly attained that there is no doubt as to the truth of the statement. In this way much of the blood pigment is eliminated in an altered form by the bile. Some, however, finds its way into the urine probably by absorption from the intestine and is there excreted in the form of urinary pigments. With the exception of urobilin these pigments (as normally met with) have not been found in or synthised from bile. But again there is no doubt that they are eventually derived in great part if not entirely from hæmoglobin.

Thus when we have a great destruction of hæmoglobin there is an overflow all round of the resulting pigments and the bile is increased and the urinary pigments also. In cholæmia there is bile pigment in the blood and only urobilin in the urine and this seems to be held up as a rather striking sign of the disease. It is so clinically but it is hardly a matter to wonder at when we realise that urobilin usually does appear in increased amount in the urine when there is any hæmolytic process going on and that even the normal process of blood destruction produces a small amount. That there is bile in the serum should again give rise to no particular surprise for this also is found in other conditions of jaundice. That it is not usually found in the urine as bile is probably due to the operation of the same agencies, whatever they are, as prevent the normal products of blood destruction so appearing. No doubt in cholæmia the agencies responsible for converting blood pigments into urobilin are as much hyper-active as is the marrow and although the normal activity might be insufficient to prevent the bile from the serum appearing as such it is easily understood that the amount of bile in the serum that would lead to bile in the urine in normal persons would not have this effect in cholæmia. That these agencies are not always sufficient for their work is shewn by the actual occurrence of bile in the urine of cholæmia when there is some very excessive bout of blood destruction as in an acute attack.

Again the absence of urobilin in the urine does not militate of necessity against the diagnosis of cholæmia, for it is reasonable to suppose that the synthesis of these pigments will sometimes proceed to the degree met with in health, *i.e.*, will only cause the excretion of urochrome. It is improbable that absolutely no urobilin should be found and statements to that effect should be qualified by mention of the steps taken to estimate its presence.

These, however, are perhaps matters of theoretical interest. The colour of the urine is usually high and bile may appear in acute attacks.

Skin.—The colour of the skin is that of a mild catarrhal jaundice. There is no deposit of pigment. The writer has seen very chronic icteric ulcers over the malleoli in this condition and these have also been reported by others. They heal after rest in bed but slowly and not very firmly. Purpura and œdema are sometimes met with.

Course.—The course of this disease is variable. It may last a life time with little alteration in intensity or symptoms. In the acquired cases it is more distinctly downhill but even the congenital are subject to attacks during which they are in relatively ill health.

In these acute attacks the liver may be enlarged, the temperature raised, the spleen larger than before, the fæces more highly coloured, the urine also more highly coloured and containing an excess of urates, and the anæmia increased. They are of varying duration and frequency. They are more severe and more frequent in acquired cases.

Duration.—This varies from a year or two to a life time—life is not shortened in congenital cases and many have reached a good old age. It must also be borne in mind that the severity of the process decreases even to total disappearance, in a certain proportion of cases.

Clinical Varieties.—These are the congenital and acquired and in addition the clinical picture differs according to whether or no the patient is suffering an exacerbation of hæmolysis at the time of observation.

The chronic cases, *i.e.*, the congenital, may present no symptoms of a subjective nature, even when all the signs of the disease are well marked, but during the exacerbations they feel ill and often appear very ill indeed. The acquired cases seldom enjoy any long period of subjective good health.

The patient may be first seen during an attack of peri-splenitis and may then present a picture which is typical only of that condition. There may be elevation of temperature, vomiting, and very great pain.

Complications.—Of these gall-stone colic and peri-splenitis are the chief. They have both been mentioned already.

Diagnosis.—This may at first present some difficulty. The Gaucher type of splenomegaly (page 131) is a familial affection in many cases and the more common type of cholæmia is also familial. The blood condition, however, differentiates the two. The ordinary type of splenic anæmia may occasionally be associated with slight jaundice even in early stage and a yellowish colour is not uncommon, but the blood changes are sufficient to differentiate the two.

Hypertrophic cirrhosis of the liver may appear as a family disease but the liver is seldom much enlarged in cholæmia and again the blood changes assist us.

Congenital obliteration of the bile duct is associated with acholic fæces as are the other varieties of obstructive jaundice.

Leukæmia and Addisonian anæmia should be easily differentiated, the former by the blood picture and the absence of jaundice, the latter by the small size of the spleen and the absence of bile in the serum as well as by the course of the disease.

Syphilis of the congenital variety may give rise to familial troubles resembling the disease under discussion but jaundice would not then be present without definite changes in the liver and the blood picture is not typical.

Cases of congenital anæmia with obstructive jaundice are differentiated by the acholic stools and the blood picture.

The blood changes are the surest single diagnostic point in all cases. Of these the relative smallness of the corpuscles and the large proportion of stippled cells and the increased fragility of the red blood corpuscles are most important.

Treatment.—The symptomatic treatment is that of anæmia and peri-splenitis, which resolves itself into the giving of iron and arsenic and rest in bed with hot applications to the abdomen.

Treatment directed to interference with the disease process itself is more complicated and of very varying success.

As already mentioned, it may be possible to detect an exciting factor and this is very commonly syphilis in the acquired disease. In such cases anti-sypbilitic treatment has a good chance of success. More rarely tuberculosis or some other infective disorder may be at the root of the disease. It is even possible for the disease to be due to intestinal infection judging from the case recorded in France in which cure of an old-standing atresia of the rectum with consequent relief to retention of fæces caused the disappearance of the typical syndrome of Cholæmia.

Various substances have been used with the intention of increasing the resistance of the red cells to hæmolysing factors. Of these cholesterin may be given in 15-grain doses in cachets three times a day or the same amount may be given intramuscularly as an emulsion in saline solution. Calcium chloride has some reputation in the same direction and is given in larger doses, *e.g.*, 60 grains per dose.

These drugs are very uncertain in action but do seem to have been of value in a considerable number of cases.

The surgical treatment of cholæmia promises to be the best and most certain. At present there are few cases with a sufficiently long history to make generalisations very safe but it may be noted that in all cases there would appear to be a sudden improvement followed by restoration of a slower nature but terminating in normal health. There are four cases in which the operation was done more than seven years ago. These deserve some mention. The first was well and had successfully passed through an attack of typhoid fever ten years after operation. He had never been anæmic or jaundiced since removal of the spleen. The second had married and had quite ceased to be an invalid after the operation. Ten years had here also intervened between operation and the last report. The third case was a sister of the last, had also married and suckled twins. Her case was reported nine years after operation. The fourth case, reported seven years after operation, was still at work, feeling very well and no longer suffering from anæmia. She suffered from mitral stenosis before the operation but this seems to be adequately compensated.

These are the only cases which the author can find in the literature and all have been strikingly successful. In the cases of more recent date there have been one or two deaths following operation. These have in every case resulted from accidents within the control of surgery, *e.g.*, sepsis.

In those cases of cholæmia where the disease is a burden splenectomy should certainly be performed—the operation is rendered more difficult and hence dangerous if delay be allowed and adhesions form about the spleen. Operation should therefore be early to get the best results.

CHAPTER XII

ADDISONIAN ANÆMIA

Synonyms.—Pernicious anæmia, progressive pernicious anæmia, Biermer-Ehrlich anæmia, megaloblastic anæmia, Infective hæmolytic anæmia, Addison's anæmia.

Definition.—A specific infection with an organism not yet isolated. The organism or its products are powerfully hæmolytic and the usual site of invasion is the alimentary tract.

Nature.—The disease is apparently due to a specific organism and is therefore entitled to the name of a specific infective disorder. It is not—so far as we know—infectious but records of more than one case in the same family are by no means uncommon. Thus the writer knows of one case in which father, mother and only son all died of the disease within a few years.

The organism is possibly a variant of the bacillus coli communis and if this prove to be the case the etiology of the disease will have to be moved one stage back when the conditions predisposing to the variation have been elucidated. We, of course, know already that the b.c.c. is subject to certain variations in virulence according to circumstances such as the resistance of the patient, the nature of the soil to which it can gain access, etc. Nevertheless we are so accustomed to suppose that we have elucidated the ultimate causation of a disease when we have identified an organism fulfilling certain conditions that the preceding conditions which lead to the arrival of that organism and his settlement are in some danger of falling outside the clinician's sphere into the domain of the medical officer of health.

General Pathology.—We do not know how the infective agent reaches the human body but the site of invasion is certainly the alimentary tract. In many cases this is obvious in the presence of an atrophic glossitis quite distinct from the tongue lesions of any other disease. The implication of the intestine is often shewn by attacks of vomiting of a severity which may be compared with the gastric crises of tabes and less frequently by diarrhœa.

The organism, having gained a footing, proceeds to multiply and in so doing elaborates toxins. These usually give rise to the first signs of disease—*i.e.*, objective signs which arouse attention from the patient or his friends. The glossitis or the lesions in the cord which will presently be described may, however, precede any signs of anæmia. Nevertheless in the great majority of cases the presence of these toxins is first shewn by the development of anæmia and this anæmia is of the type which we know to follow the destruction of blood in the circulation. Why the particular blood picture which we associate especially with this disease should follow intra-vascular destruction of blood is not yet determined, but as far as we know at present it depends on the rate at which the destruction takes place and on the presence in the body of the products of blood destruction which seem to have a particularly powerful influence on blood regeneration.

The organism does not, however, go on multiplying indefinitely but after a while succumbs either to the resistance developed by the host or, as is perhaps more likely, to the products of its own multiplication. There is then a cessation of hæmolysis and the patient recovers from the attack and often goes back to work. Then, once more, the defensive powers of the host fail or the self-destructive bacterial products are excreted and the organism again becomes active. The patient has a relapse which may be fatal or may be followed by another remission. With proper treatment each remission may be less severe and eventually they cease to occur at all and the patient is cured. If treatment is at all half-hearted or intermittent cure will not occur and the second or third attack will prove fatal. The disease is often aggravated by the existence of a septic condition of the mouth. This, of course, is not the same thing as the glossitis above referred to although there is a very widely prevalent misconception to that effect. The feature which makes oral sepsis so serious in Addisonian anæmia is the presence of lesions caused by the specific organism which allow of the absorption of the septic poisons of the common organisms responsible for the oral sepsis. These poisons are inhibitory of blood formation, as is seen in the anæmia of any septic condition and consequently the more dangerous when—as in the disease under consideration—there is need of rapid blood regeneration to make up for hæmolysis.

Allied Diseases.—All hæmolytic anæmias (*q.v.* page 191) present analogies with Addisonian anæmia and many severe anæmias of other types may show a similar blood picture but lack other features of resemblance.

The question of how nearly lymphæmia and myelæmia are allied to Addisonian anæmia is one of great interest, for our knowledge of the etiology of the latter might be of assistance in determining the cause of the former. The features which they have in common may therefore be briefly enumerated. In all three diseases there is a great increase in the red marrow—*i.e.*, that part concerned with blood formation in contrast to the inactive yellow or fatty marrow. In all three diseases there is clinical evidence of the greatly increased destruction of blood cells—in Addisonian anæmia of the red cells, in the other two of the white cells. In all three diseases the number of cells in the blood stream is determined by the relation of cell formation to cell destruction. According as one or the other has the predominance the number of cells in the blood stream will be above or below normal and the variations far exceed those of health. In all three diseases the excess of cells is largely formed of immature and abnormal cells. All three diseases are prone to relapses and remissions often independent of treatment and all are much improved by the administration of arsenic. Moreover in lymphæmia and myelæmia, but especially in the latter, the blood picture as far as the red cells are concerned may be that of Addisonian anæmia and there may be the same excess of iron in the liver.

These points are too many not to have some significance and it would be by no means surprising to find that the increased cell destruction was the primary blood lesion in all three diseases and responsible for calling into being the overgrowth of the marrow. These matters are as yet, however, mere conjecture.

Etiology.—Since the disease is almost certainly due to the activities of a micro-organism it is sufficiently obvious that any factor generally recognised as predisposing to the onset of bacterial infections may be regarded as among the etiological factors of Addisonian anæmia. Of these there are a very large number and each has been hailed in one case or another as the causa causans of the disease. That can hardly be the case but we may reasonably allow them a place amongst the predisposing factors. The most important of them are hæmorrhage, and prolonged residence in unhygienic circumstances.

The exciting cause is the growth and development of the causal organism. There is evidence to suggest that this is a denizen of the intestinal tract—perhaps of the whole alimentary canal. There is also reason to suppose that it will prove to be a member of the large family of which the colon bacillus is the best known. A member of this family has, indeed, been isolated from cases of Addisonian anæmia which has hæmolytic properties and produces in animals a disease not to be distinguished from Addisonian anæmia. That it produces an apparently identical disease in animals does not, of course, prove that it is the prime etiological factor in man of Addisonian anæmia but the fact is very suggestive.

Allowing—as the most useful working hypothesis—that the disease is caused by an intestinal organism we shall naturally scrutinise closely the state of the digestive system when cases present themselves. By so doing we shall be able to cure a certain proportion of cases and as our methods of combating intestinal sepsis become more perfect a very large proportion if not all.

Age and Sex.—It is a disease of the adult and occurs at about that period of life when cancer has its greatest incidence. There is no great difference in the sex incidence but there are, perhaps, more males than females affected. It is difficult to say for certain, as under the title "Pernicious Anæmia" it has been confused with various toxic, traumatic and helminth anæmias. For the same reason little can be said about the occurrence of the disease in children—most of the alleged cases do not bear close scrutiny. There is, however, no reason so far as we are aware why children should not be affected and in consequence the possibility should be borne in mind.

Onset.—Clinically the onset of this affection is gradual and not infrequently the patient's friends notice the anæmia before the patient himself. The victim of the disease probably notices increasing disability to do his work, although in quite a number of cases work is possible and even performed as well as usual when the anæmia is very severe. The latter fact accounts for the infrequency with which the early stages of the disease come under the notice of the physician.

The onset may exceptionally take other forms and of these a sore tongue is the commonest. The soreness is often appreciated by the patient and brings him for advice but in some cases the obvious glossitis does not seem to cause any subjective annoyance.

Nervous symptoms are, perhaps, more often talked about than seen and this is very largely due to the fact that they are not looked for. They are mentioned here because paralysis sufficiently extensive to confine the patient to bed may be the first sign of the disease which subsequent developments show to be Addisonian anæmia. The nervous symptoms may stimulate almost any disease of the nervous system, *e.g.*, tabes dorsalis, peripheral neuritis, etc.

A sudden profuse hæmorrhage is an uncommon but not unknown first symptom. This may take place from the nose or stomach or from some less usual site such as the inner ear or even from the conjunctiva.

General Symptomatology.—The symptoms of anæmia usually dominate the clinical picture and these are not different from those seen in any other form of anæmia and need not here be specified. Occasionally the gastric disturbance is most prominent, occasionally the nervous. These also will be more fully discussed later.

Nervous System.—The type of severe nervous disorder associated with Addisonian anæmia is that known as combined sclerosis. It depends on actual lesions of the nervous system—of the nature of degenerations—demonstrable after death. The foci of sclerosis or softening are found in various parts of the cord and the symptoms vary accordingly. Thus there may be an increased knee jerk and well-marked spasticity or an absence of the knee reflex and ataxia. Again, though rarely, the symptoms may be those of peripheral neuritis. When the latter is the case it must be borne in mind that arsenic produces similar symptoms. The subjective symptoms vary in the same way according to the extent of the affection of the sensory paths.

It is, however, only rarely that the nervous symptoms predominate over those of the anæmia or give rise to a typical combined sclerosis. It is far more usual to meet with slight disorders of sensation such as numbness, formication or tingling. There may in the same way be slight motor disorders and it may be difficult to say how much is due to weakness directly traceable to the anæmia and how much to the toxic principle which causes the nervous symptoms and the anæmia alike.

Mental symptoms are not uncommon especially towards the close of the patient's life and of these the commonest are conditions of stupor and impaired consciousness. Excitement of a degree worthy of the term mania is very infrequent but may occur and may even necessitate mechanical restriction of the patient's movements.

Such in brief are the nervous symptoms of Addisonian anæmia and it is not the purpose of this book further to elaborate them. Every case will be found to be a law unto itself and the capacity for surprise if—as is hardly probable—at all well developed in the medical attendant should be kept in abeyance.

The possibility of hæmorrhages affecting some part of the nervous system and giving rise to unusual symptoms provides a further reason for the last sentence.

Olfactory System.—There is here nothing of note to record—perversion or loss of the olfactory sense might of course take place but one can hardly imagine it as a prominent feature of the disease.

Auditory System.—This is more likely to be affected than the last but is still not very often likely to call for the physician's attention. Hæmorrhage may take place into the internal ear and be followed by deafness but it is much more common for the auditory symptoms to be referable to the anæmia, *i.e.*, buzzing and noises in the ears owning no obvious physical basis. Extraordinary as it may seem it is nevertheless a fact that fatal hæmorrhage may take place from the external ear.

Ophthalmic System.—Defects of sight are fairly common but whereas retinal hæmorrhages are said to be present in over 80 per cent. of cases it must not be supposed that so large a proportion will complain of failing vision. The absence of retinal hæmorrhages would be a point against the diagnosis of Addisonian anæmia in a doubtful case. Besides retinal hæmorrhages there may be optic neuritis or even optic atrophy but the ophthalmic system does not seem to have been studied so critically in Addisonian anæmia as it has been in cholorosis and there are few available records of these complications. There can be no doubt that atrophy is very rare and optic neuritis not nearly so common as retinal hæmorrhages.

Very rarely hæmorrhage into the optic nerve or into some part of the optic tracts may give rise to symptoms. The latter, of course, vary with the position of the hæmorrhage.

Circulatory System.—The heart is almost always affected with a variety of fatty degeneration known from its appearance as "tabby-cat striation." This is an excellent name for the appearances seen but it is quite certain that the condition is not peculiar to Addisonian anæmia although more constant in this condition than in any other. The fatty change affects the muscle fibres themselves and after a time leads to dilatation of the heart with all its clinical signs and unpleasant consequences. The extraordinary way in which some cases when apparently at death's door recover and return to an active life suggests that this fatty change may be largely recovered from—possibly by a compensatory hypertrophy of the unaffected fibres and possibly by the restoration of the fatty fibres to their normal integrity.

Symptoms referable to the heart will vary according to the condition of that organ and in consequence almost any condition may be apparent clinically. It will therefore serve no purpose to detail information which is a commonplace of medical practice. There is no clinical heart condition with any claim to be peculiar to Addisonian anæmia.

The vessels in this disease partake of the same fatty change as is present in the heart and in consequence hæmorrhages are far from uncommon. These are both large and small—the latter are often very numerous and so minute as to give no sign of their existence clinically—they have served as a basis for a theory which seeks to explain Addisonian anæmia as largely due to their presence. They have no other importance clinically. The larger hæmorrhages are comparatively infrequent—quite infrequent as compared with leukæmia. When present they take place perhaps most frequently from the nose, not from the small spot on the anterior part of the septum but from less accessible places at the upper and posterior portion of the nasal fossæ. They may lead to death from apoplexy, may take place into the alimentary tract and give rise to hæmatemesis or melæna, or may be first seen as hæmaturia, menorrhagia or inter-menstrual bleeding.

The treatment of these hæmorrhages does not differ from that of hæmorrhages in other conditions and will be found fully dealt with on page 338.

Spleen.—This is little if at all enlarged and cannot usually be palpated. Post mortem it presents a contrast to the other organs, being dark red as a rule and congested instead of bloodless and pale. Microscopically it shows signs of extensive blood destruction in the presence of excess of pigment and phagocytosis of red cells.

Marrow.—This is dark red and often semi-fluid. Microscopical examination shows the presence of large numbers of nucleated red cells of varying shape, size, and hæmoglobin content. There is also relative diminution of the leucocytes.

The most notable fact about the marrow is that it is found even in an adult to occupy the shafts of the long bones showing that there has been a great increase of this tissue at the expense of the fatty tissue usually found in the shafts of the long bones in adult life.

Blood.—In a typical advanced case the condition of the blood is very striking but the suggestion that the disease can be diagnosed by an examination of the blood alone is fallacious and merely indicates that those who make it do not trouble to differentiate the various types of severe anæmia with their varying prognosis and treatment. Owing to certain theories which have travelled across the North Sea in considerable force this error is a very common one but is being gradually dispelled. It is, of course, true that the "pernicious anæmia" type of blood presently to be described is more commonly met with in Addisonian anæmia than in any other disease but it is equally true that it may be met with after hæmorrhage, in cancer, in those who have been poisoned by certain drugs or their fumes, in many septic troubles, in leukæmia and in a variety of other conditions.

We may now proceed to consider the changes in the blood on which it was customary to found a diagnosis of "pernicious anæmia"—a term of which the significance varies so much with different people that it is impossible to retain it.

The red corpuscles are commonly much reduced in number when the patient is first seen—comparatively frequently below 1,000,000 per c.m.m. In consequence the blood appears pale, yellowish and of undue fluidity: it forms a poor clot which is quite unable to close the mouths of bleeding vessels and there is consequently a spurious hæmophilia.

Examined under the microscope the cells are seen to vary a great deal in size—the majority appearing larger than normal. At the same time there are large numbers of very small cells, some of them appearing to be fragments chipped off the larger ones. Further examination shows that the cells vary not only in size (anisocytosis) but also in shape (poikilocytosis). The commonest type is of an oval shape but the most striking shapes are naturally the most distorted. Of these many are pear-shaped or resemble the mark left on a new wall paper by a splash of water. There is no limit to the bizarre shapes which may be met with.

When a film is stained—all the above changes can be seen without so doing and are usually apparent in the counting chamber—it is noted that many of the corpuscles seem to stain more darkly than normal and this is rightly conjectured to be due to their greater hæmoglobin content.

In addition, presuming that a double or triple stain has been used, certain other peculiarities will be noted in the red corpuscles. Of these the two known as polychromasia or polychromatophilia and basophil granulation or stippling will be first considered although of less importance than the third, *viz.*, the presence of nucleated red cells.

Polychromasia implies that the red cells, instead of taking only the red or acid stain, take up also some of the blue. This gives them a dusky or even a bluish appearance. It probably indicates that the cells are not fully mature and is thus indicative of considerable strain on the functions of the bone marrow.

Stippling is the presence of blue or black dots in the envelope of the red cells. Its exact significance is the subject of theories and need not be here considered as it has no clinical value in a case of Addisonian anæmia, although of great importance in lead poisoning (*q.v.*, page 371).

Nucleated red cells are common but not invariable in Addisonian anæmia. They vary in size and staining reaction as do the non-nucleated red cells already discussed. The nuclei vary in size from dimensions much smaller than those of a red cell to twice the size. They vary in their capacity for taking up stains. Some stain more deeply than any other nuclei met with in the blood, but many of the larger nuclei stain very poorly and are with difficulty identified. The significance of nucleated red cells is twofold. They portend that the marrow is highly active and therefore that the resistance of the patient is still maintained but the fact that they are present also signifies that the call on the marrow is urgent and the blood loss extensive so that the probability of that tissue being tried beyond its capabilities is by no means absent. The prognostic significance of the presence of nucleated red cells is therefore nil but the prognostic significance of their absence in a case of severe anæmia is considerable and grave.

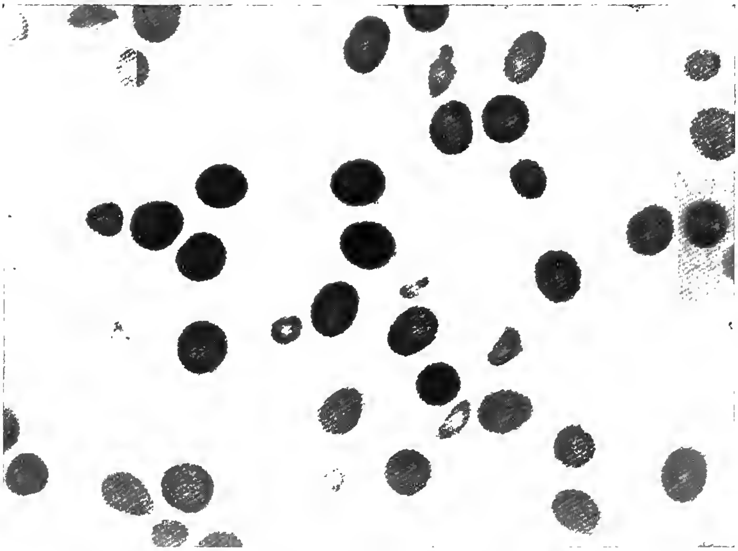


FIG. 33.—Microphotograph of the blood in a case of Addisonian anæmia shewing many megalocytes and microcytes. The former are of an oval shape and obviously contain an unusually large amount of hæmoglobin. The oval shape is very characteristic. The microcytes shew various differences in shape, *i.e.*, poikilocytosis.

The idea that the fact of there being large nucleated red cells with ill-staining nuclei (megaloblasts) present in the blood had any particular significance from a diagnostic point of view is not now entertained by those who have made most study of the matter in this country.

For the significance of the presence of nucleated red cells in the blood in other diseases see also page 183.

If the blood be examined fresh and the wet film studied for some time changes in the cells of the nature of vacuolation may be seen or these may be observed to have taken place in the stained film. This is a degenerative change. The hæmoglobin percentage in a typical case of Addisonian anæmia is higher than that of the red cells and in consequence the colour index is above unity. It may be as high as 2 per cent. or even higher—but it may also be below unity so that too much reliance cannot be placed on this point.

The white cells are always diminished in Addisonian anæmia unless it is complicated by some septic process of sufficient intensity to cause a leucocytosis on its own account. This is seldom the case—oral sepsis is not a process of sufficient intensity to do so.

The diminution affects the marrow-formed cells, *i.e.*, the polymorphonuclear leucocytes and in consequence the numbers of lymphocytes appear high. This is a relative and not an actual increase and the number of lymphocytes per c.m.m. as distinct from their percentage will be found to be normal or subnormal.

A few myelocytes may be present. Except as suggestive of the profound change in the bone marrow they have no particular significance.

The above description of the blood changes in Addisonian anæmia is to be understood as applying to the majority of advanced cases. It does not apply to less severe cases and as recovery takes place the appearances met with in the blood return to normal. Every intermediate stage may be met with and Addisonian anæmia cannot be excluded by examination of the blood, by the absence of a high colour index or of poikilocytosis.

It is very important to remember that the blood changes are only one feature of the disease, an important one but not of the overpowering significance that has sometimes been attributed to it. It may be compared to the physical signs of consolidation—they are of considerable importance in confirming a diagnosis of lobar pneumonia but are not themselves sufficient grounds for making such a diagnosis in, for example, an afebrile active patient, nor is it impossible to have a lobar pneumonia in which consolidation cannot be demonstrated nor is it present at all stages of pneumonia.

Variations in the specific gravity, salt content, volume, etc., of the blood are not yet important from the clinician's point of view although of considerable theoretical interest.

Urogenital System.—There is nothing here to note except the occasional occurrence of hæmorrhage. The urine is discussed subsequently.

Lymphatic System.—The lymphatic glands show no changes.

Osseous System.—Apart from the changes in the marrow there is little to note—there may be tenderness over the bones especially if the hæmolysis has been severe.

Muscles.—These are normal or, in some cases, wasted. They are like most other organs—pale and bloodless.

Skin.—The characteristic change in the skin is a yellow or primrose colour which must be seen to be appreciated—no verbal description would be of any value but it may be noted that the colour is not so transparent as that of chlorosis nor so yellow as that of cholæmia and jaundice. It is best described as a primrose colour.

Pigmentation is rare—it may occur after the administration of arsenic but when due to the disease process itself is often more manifest in the mucous membranes than in the skin. It seems to have no particular partiality as regards extent or position beyond this. A diffuse pigmentation is less common than that form which appears as scattered spots of varying intensity.

In a few cases ulcers have been present over the malleoli and these are apt to be very intractable.

Purpura is uncommon but may be met with.

Glands.—The ductless and other glands are normal except those of the intestinal tract.

Respiratory System.—As would be expected dyspnœa is often present but it is not often well marked and may be absent even when the anæmia is severe and the heart condition very serious.

Hæmorrhages may occur from or into the lungs but neither are common, hæmorrhage from any part is not nearly so frequent in Addisonian anæmia as in many other varieties.

Post mortem œdema is found and the lungs are white and bloodless but there is no feature characteristic of the disease.

Alimentary System.—The first point of note is the condition of the tongue. This—in many cases but not in all—exhibits a variety of glossitis which has some claim to be pathognomonic of the disease. It may, however, be met with in other conditions but is very rare. The papillæ are uniformly wasted and shrunken so that the tongue has a generally smooth and atrophic appearance. This appearance is especially well seen at the edges and may be hidden by fur elsewhere. The smooth and glistening surface may be here and there interrupted by red patches of superficial ulceration but these are not invariable.

There are often subjective sensations of soreness or of an unpleasant taste in the mouth and these may precede any marked naked eye abnormality and any appearance of anæmia.

Microscopically the atrophy is well marked and the deeper layers of the tongue may be seen to be invaded by organisms. The evidence that these are the causal organisms of the disease is not clear, but it may be that they are, and vaccines made from tongue organisms during life have been used with some little success.

The stomach may be the seat of similar changes and they are there more constant than in the tongue. Microscopically the glands are seen to be atrophied and degenerate and there may be organisms in the deeper layers of the mucosa. In severe cases there may be practically no mucosa and the stomach wall may appear almost transparent and as thin as paper. The intestines may present a similar appearance—to an extent seldom met with in any other disease with the single exception of sprue. The latter, of course, is hardly likely to give rise to very frequent difficulties in diagnosis in this country.

There are no changes in the stomach or intestines that can be said to be absolutely characteristic of the disease but the presence of considerable atrophy is distinctly in favour of a diagnosis of Addisonian anæmia.

Other lesions may be found but are not to be understood to bear a relation as direct as that of the atrophy to the anæmia. These include ulceration of varying degrees and in various situations. Ulcers of the small intestine are common but are usually microscopical and partake more of the nature of denudation of the surface over extensive areas by atrophy of the mucosa. Larger and deeper ulcers may be found in the cæcum—as they may be in several wasting diseases. Cancer is an extremely rare complication.

Finally it may be noted that hæmorrhages may occur from any portion of the gastro-intestinal tract.

Liver.—The liver may be enlarged but not to any great extent. The chief change in this organ is only to be demonstrated after death. It consists in the presence of iron deposits. The liver surface turns blackish on application of ammonium sulphide.

The significance of the iron is obvious when we remember the large share which the liver takes in disposing of the products of hæmolysis. The pigment which contains the iron is proportional in amount rather to the severity than to the duration of the disease. This is due to the fact that small quantities of disintegrated hæmoglobin, although frequently renewed, can be dealt with while a sudden large influx leads to a large accumulation which is only slowly eliminated.

Fatty degeneration of the liver is common.

Urine.—The urinary changes are of some importance. They are two in number. The first is excess of urobilin. If a spectroscope is available the excess is easily demonstrated by the depth of the urobilin band about the E line. Otherwise it may be tested for by making the urine ammoniacal with ammonia and then adding a 1 per cent. alcoholic solution of zinc chloride. This gives in a few minutes a green fluorescence which is quite unmistakable. It may be necessary to filter the mixture before this is apparent.

Failing either of these methods the colour of the urine is of assistance and in most cases will afford a fairly reliable measure of the amount of hæmolysis. The colour is usually rather orange than yellow and far deeper than normal although the amount of the urine is not diminished. It will often be found that an increase of severity in the symptoms coincides with an increased depth of colour in the urine.

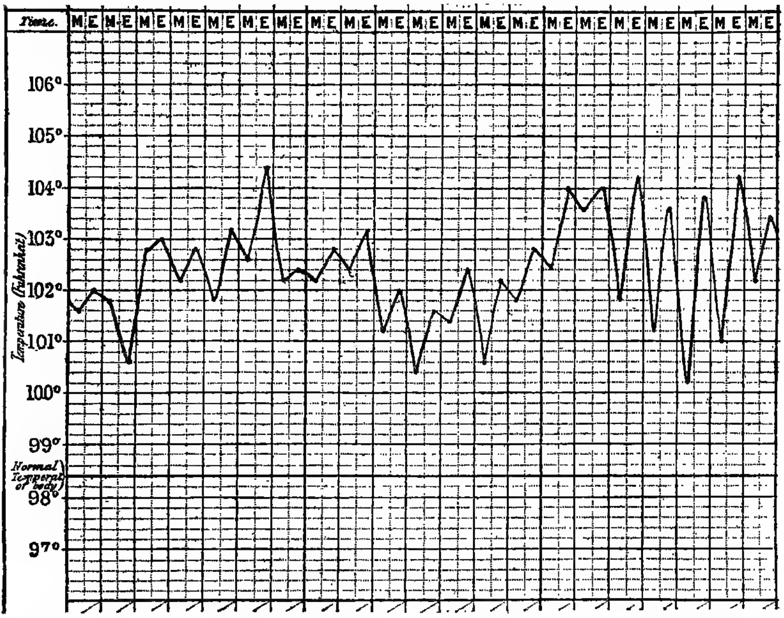


FIG. 34.—Three weeks' chart of a severe case of Addisonian anæmia showing continuous pyrexia such as is not uncommonly met with.

The second change is the finding microscopically of minute yellow granules in the urinary deposit. These represent altered hæmoglobin and are also indicative of hæmolysis. Their importance lies in the fact that they are not found in other conditions associated with urobilinuria and so may prove of diagnostic value.

The amount of urates, etc., varies and is not of importance clinically.

Metabolism.—There are two disorders of metabolism of importance or perhaps three. The first is the increased hæmolysis with the urinary changes which follow it—these have been already described. The second is the result of malassimilation. It is suggested sometimes by an extraordinarily large appetite, sometimes by wasting, seldom marked and seldom absent. The third includes the changes due to fever and these—concentration of the urine, etc.—are not different from those met with in other febrile cases. The metabolism of Addisonian anæmia is chiefly of importance from the point of view of diet and was discussed under that heading (page 235).

Fever.—This varies so greatly that no definite type can be laid down. The temperature may rise to as much as 105° F. but this is not usual. It is often subnormal. It is apt to be elevated when the hæmolysis is most severe and nearer normal in the intervals of less severity.

Course.—The course of this disease is very peculiar and is marked as a rule by at least one remission. The transition from remission or health to disease is slow but the transmission to health or remission is often dramatically sudden. The patient one day seems moribund, will take no nourishment and is hardly conscious—on the next he demands a chop, sits up in bed and manifests every sign of interest in his surroundings that was absent before. This is not always the case but when it does occur is a most striking feature of the disease. A normal condition of health judged by the degree of the anæmia is of course not so quickly attained as the subjective sensation of well-being and may take many months. As is discussed under treatment this slow recovery of the blood is of some importance.

Cases with acute onset may progress rapidly to a fatal termination with no sign of remission but the majority of cases have one such period and some more.

As one remission succeeds another the patient's condition is left less favourable than before until the next relapse as it were overtakes the remission and he dies. The remissions are shorter and shorter as their number increases. With adequate treatment the relapses, on the other hand, are further and further apart and of less and less severity until they cease to appear and the patient is cured. The later relapses, *i.e.*, the third or fourth in these cases may not confine the patient to bed and would pass unnoticed if it were not for the examination of the blood periodically—a wise precaution in all cases.

Duration.—This varies from a few weeks in acute and severe cases to some three or four years in less acute. In addition there are quite a number of cases in which the relapses are separated by five to ten years—there is on record the case of a man who died in a "relapse" thirty years after his first attack. There had been no intervening attacks. It is obviously doubtful how far one is justified in referring to this as a relapse—it ought probably to be called a second attack in a cured patient.

If the physician is asked the probable duration of an individual case he had better seek refuge in non-committal platitudes than adventure anything definite. He cannot know the probabilities except inasmuch as a very acute onset is less favourable than a very chronic one.

Remissions are of variable duration—three to six months is an average time according to the severity of the case and the degree of recovery.

Relapses do not last so long as the original attack.

Clinical Varieties.—These are the acute and chronic and the nervous types. The acute variety is distinguished by the greater rapidity of onset and termination and is more liable to hæmorrhages than the other. It is more apt to be met with in younger persons than in their elders.

The chronic variety is the common one and the first symptom may neither be anæmia nor suggest it. Thus profuse hæmorrhage may be the first sign or fainting attacks or severe vomiting or severe pain in the stomach without vomiting. Its course has already been indicated.

The nervous variety is dealt with under Nervous System on page 239. It is important to remember that the nervous symptoms may precede the anæmia.

Complications.—The commonest as it is the most dangerous complication is sepsis. Septic processes tend to depress the activity of the bone marrow and it is therefore obvious that they are peculiarly dangerous in Addisonian anæmia where great activity of the bone marrow is necessary if the excessive hæmolysis is to be adequately compensated.

The commonest septic foci are the mouth and intestines. The latter has been in part dealt with already and the subject of oral sepsis is more fully dealt with under Secondary Anæmia. It is only necessary to remark here that oral sepsis or sepsis in any other part of the body cannot of itself cause Addisonian anæmia—unless the ravages of the organism which is presumed to be at the root of the disease are considered septic processes. Perhaps it would be better to say that it is impossible for the common pyogenic organisms or the organisms of an ordinary case of gingivitis and pyorrhœa to cause Addisonian anæmia. It is not a fact that William Hunter has put forward this latter view, although that misconception has an extraordinary prevalence. His view of the rôle of oral sepsis in the disease is that put forward above and it has been plain for all folks to see in his various books on the subject of anæmia—books to which students of this fascinating subject are deeply indebted and to which many patients who have never heard his name have every reason to be most thankful.

The symptoms more fully dealt with under the Nervous System (page 239) are not to be regarded as complications although commonly referred to as such. They are so far as we know directly due to the toxins produced by the causal organism and are thus part of the disease process.

There are no other complications of particular importance although various intercurrent diseases may, of course, occur.

Diagnosis.—Below are detailed some of the chief features of Addisonian anæmia. They are divided into three groups—hæmolytic, gastro-intestinal and toxic. Where there is no apparent cause for an obviously hæmolytic anæmia and where there are symptoms suggesting a toxic cause it is extremely probable that we are dealing with an example of that peculiar type of anæmia which Addison described and to which his name is appropriately given. If there are gastro-intestinal symptoms and especially if there is a condition of atrophic glossitis the presumption becomes as near a certainty as the present imperfect state of human nature allows.

Features due to hæmolysis:

1. The presence of urgent reaction of the bone marrow shewn in the blood by the presence of nucleated red cells, poikilocytosis, megalocytosis and increased hæmoglobin content of each corpuscle.

2. The presence of an abnormal amount of urobilin in the urine which latter is usually of a high colour although the amount is not diminished.

Symptoms referable to the alimentary canal:

3. A smooth pale tongue, perhaps showing raw red areas and often painful.

4. Persistent gastric pain sometimes fully as severe as the crises of tabes dorsalis and showing no disposition to yield to treatment—usually associated with frequent vomiting and often disappearing as suddenly as it came. The subsidence of this symptom may be quickly followed by great improvement in the patient's condition.

5. Similar intractable diarrhœa, disappearing in the same way.

Toxic symptoms:

6. Fever.

7. Delirium or other altered mental condition.

8. Combined sclerosis.

It will be noticed that the yellow colour commonly seen is not mentioned. It is not characteristic of any one variety of anæmia and is especially apt to be present in the anæmia of gastric cancer with which Addisonian anæmia may be easily confused. The different prognoses in the two conditions renders this mistake very unfortunate.

Now as regards the conditions with which Addisonian anæmia may be confounded. The first is leukæmia. In 99 cases out of 100 the mistake is impossible but that it may be made the literature of the past twenty years bears witness. The difficulty arises from the occasional occurrence of cases of leukæmia which do not show a typical blood picture and in which the glandular enlargement is slight or splenomegaly not a prominent feature. The opinion of an expert is perhaps the only way out of the difficulty if the blood findings are equivocal—but expert opinions on the blood are not nearly so valuable as ordinary clinical observations. If the spleen is palpably enlarged, *i.e.*, if it can be felt to come below the level of the ribs in the recumbent position the diagnosis of Addisonian anæmia is unsafe. Addisonian anæmia will not account for enlargement of the glands—however slight—and Addisonian anæmia is very rare in children while leukæmia, by comparison, is common. If these few points are remembered the hundredth case will be as correctly diagnosed as the ninety-ninth.

Cancer of the stomach may show practically no physical signs except anæmia and these cases give rise to considerable difficulty, particularly as the gastric symptoms may be the same in cancer and in Addisonian anæmia. There are, however, some few points which should enable a correct diagnosis to be made in every case. It may be laid down as a rule that gastric cancer of a degree likely to cause confusion with Addisonian anæmia always has a relative and usually an absolute leucocytosis, while Addisonian anæmia never has. The exception necessary to prove this rule is the case of Addisonian anæmia complicated with some septic factor, *i.e.*, with septic absorption of considerable intensity such as is seen in pneumonia. This case will not very often be met with and even then it will not as a rule be the case which presents any difficulty in the differential diagnosis from gastric cancer. Another point but a less certain one is that there is usually more wasting in cancer than in Addisonian anæmia. The presence of a tumour revealed by palpation or the X-rays will decide the diagnosis.

Anæmia due to parasitic worms may closely simulate Addisonian and under the unfortunate title of pernicious anæmia the two have been grouped together—with a large variety of other anæmias.

The resemblance may extend to a similar blood picture but this is not nearly so common as the literature might lead one to believe. It is almost if not quite unknown in this country. The fact that it may occur and so lead to confusion makes it the more necessary to exclude all possible causes of anæmia before diagnosing Addisonian. In the case of parasites it is best done by means of an anthelmintic if examination of the fæces with the microscope is not practicable. The history of residence in a foreign climate will cause one to be on the lookout for this sort of disease.

Anæmia due to hæmorrhage will not usually give rise to difficulties but it may do so. It occasionally happens that false modesty conceals menorrhagia or metrorrhagia. It may even hide hæmorrhoids—the writer has seen at least one case in which the diagnosis of Addisonian anæmia was erroneously made in consequence. It is the physician's duty in any case of anæmia to enquire whether there has been any loss of blood. Where the blood is lost by internal bleeding, *e.g.*, from a duodenal ulcer, the difficulty of diagnosis may be increased by the high colour of the urine following the absorption of some of the blood. The blood examination will usually enable one to clear up any points which the clinical investigation has left obscure.

There is a form of secondary cancer of bone in which the blood condition may be rather peculiar and this may lead to a diagnosis of Addisonian anæmia when that disease is as a matter of fact not in evidence. The history of a primary cancer, *e.g.*, of the breast removed by operation or the presence of a visible tumour in any situation will almost always keep one from going wrong. The matter is further mentioned under Cancer of Bone (*q.v.*, page 361).

Chlorosis ought not to give rise to difficulties but if it should it will be in a case of relapse with a history of anæmia about the time of puberty or else in a patient suspiciously young for Addisonian anæmia. The blood examination as well as the results of treatment will give the desired information in case of doubt.

Addison's disease of the suprarenals is characterized by pigmentation and the latter may also be present in Addisonian anæmia. In both there may be some pallor. There the analogy ends as a rule and if it should seem to go further a blood examination will be required and will be conclusive in the vast majority of cases.

These are the principal conditions with which Addisonian anæmia is likely to be confused, although if the blood picture be made a diagnostic sign of first importance other conditions should be added.

Treatment.—This must be dealt with under several headings but certain remarks of a general nature may be first mentioned. The surroundings of the patient should be noted and if unfavourable an attempt should be made to modify them. As is the case in all other types of anæmia light and air are of the first importance. In hospital a patient should have the sunnier side of the ward, in private a south aspect is better than another. Open air treatment is not usually prescribed for anæmia but is most certainly a valuable accessory and should be employed as far as the circumstances of the patient allows. Anæmic patients are apt to feel cold and this must be remembered. The value of fresh air is that it implies that the air is frequently changed and therefore the little hæmoglobin available does at least get access to all the air it needs instead of to the contaminated atmosphere of many dwelling houses. Fresh air also gives a sense of well-being to the patient which is of value—if there is one thing surer than another in treatment it is that the mental attitude of the patient often has more to do with cure than one can find a ready explanation for.

Rest.—By rest is meant rest in bed—permission to lie on the sofa means permission to do anything else the patient has a mind to and often implies a waste of energy which can be ill afforded. In a disease where the basis of all metabolism, *i.e.*, the red corpuscle is defective it is good policy to call for as little metabolic expenditure as possible. If rest in bed after a few days' trial appears to make the patient so restless and unhappy that one feels doubt as to whether it would not be better to let her up, drugs of a sedative nature are permissible. The synthetic aniline preparations such as acetanilide, phenacetin, etc., are not to be employed nor are the sulphonal, veronal and trional group. Liquor Morphinæ Bimeconatis in doses of dr. 1/2 to dr. 1 may prove of value and failing this the bromides can be used. Restlessness does not as a rule cause any difficulty in Addisonian anæmia since the average patient is only too glad to get to bed. Nevertheless when the blood pressure is low, agitation is not infrequent and needs treatment.

Asepsis.—It has already been explained that any septic process tends to depress the activity of the red marrow and that it is therefore necessary to remove any septic focus as soon as possible. This is a good and much neglected rule in any disease but it is essential to success in treating Addisonian anæmia that it should be paid more than lip service. The commonest septic focus is in the mouth and takes the form of caries and gingivitis. Pyorrhœa is usually associated with these. The subject of oral sepsis is dealt with in several places but it needs to be mentioned again here as there is a great tendency to put off operations for the removal of septic foci until "the patient is a little stronger"—which time often fails to arrive. It is much better to let the patient lose a little blood by hæmorrhage from a tooth socket than to let him keep his septic focus. Extraction is the only way of dealing with pyorrhœa alveolaris in such a disease as Addisonian anæmia—in other conditions, *e.g.*, chronic arthritis, it may be permissible to dress the teeth and administer vaccines, in the disease under consideration the best way is the quickest.

Supposing that on very careful examination the teeth and gums are found to be in good condition and actually free from sepsis, it is next necessary to look for other possible sources of infection. Of these the nasal cavities, tonsils, accessory sinuses and middle ears deserve attention. As a rule these will be found in good condition but it is well to remember possibilities.

If there does not seem to be any septic focus about the head there may be vesical or parametric trouble. These also will require to be dealt with—it is not justifiable to do an extensive operation in such cases so that it will often prove more desirable than possible to deal with the last complications in the few cases in which they may arise.

Intestinal sepsis is a difficult but essential problem of the disease. Its solution rests to some extent on the nature of the diet which will be discussed immediately. It may also be attained—or rather its attainment may be hastened—by the use of drugs. One of the natural antiseptics, viz., hydrochloric acid is notably deficient and this must be compensated for. Hydrochloric acid may be conveniently administered well diluted with mucilage water and large doses should be given. Five minims of the strong acid may be given three times a day fifteen minutes after food and repeated again fifteen minutes later. The patient may even take a drachm of the strong acid daily without harm. Washing out the stomach is also a useful method of attaining aseptic conditions but is very often not well borne and must always be employed with extreme caution owing to the atrophic condition of the stomach. Rectal lavage is more generally applicable and useful.

Certain drugs, particularly the salicylates and their derivatives such as salol may prove useful. There are some grounds for supposing that arsenic is also a good intestinal antiseptic and it is therefore as well to administer this drug by the mouth rather than hypodermically. It is in any case excreted in the large intestine and so may exert its antiseptic action there however it is administered.

The administration of lactic acid bacilli—the sour milk treatment—is of theoretical value and has as a matter of fact proved of considerable advantage in practice.

Finally it is of obvious importance if intestinal asepsis is to be ensured that the bowels should be opened regularly. For this purpose liquid paraffin in doses of 1 to 2 drachms daily is often sufficient and enemata should be employed in obstinate cases. The commoner and rather drastic purgatives, as calomel, cascara, etc., are not to be used if they can be avoided—but mag. sulph. is very useful—possibly because it is excreted by the colon.

Diet.—This is a very important factor in the treatment of these cases. It will sometimes happen that the patient has an extraordinary good appetite—he will eat enormous amounts of food per diem with the greatest avidity. This means that he is not assimilating well and the large bulk of the food remains undigested to form a nidus for the growth of undesirable organisms and the promotion of intestinal putrefaction. These large appetites are therefore not so much a matter of congratulation as the laity do sometimes ignorantly suppose.

One of the first things to remember about the diet is that it ought to be readily digestible. The digestive glands are atrophic and in consequence the digestive juices lacking. These must therefore be caused to act on the food before it is taken, *i.e.*, the food must be peptonised.

The bulk of the food should be the smallest possible for the greatest nutritive value. This is an indication for the avoidance of all food which leaves a solid residue of an unassimilable nature. Thus fruit is best avoided and such vegetables as are chiefly composed of stalks. Proteid in the form of eggs is of great value and as many as a dozen a day may be taken if individual idiosyncrasies allow. Such a large number must of course be given in many meals at short intervals and the stomach must not be overloaded.

It must be remembered that albumens such as those of egg are good food for putrefactive organisms if not digested so that signs of intestinal putrefaction should be looked for from time to time if many eggs are being taken. If this is the case the fæces will smell offensive and the urine may contain excess of indican. Indican may be tested for in the following way. To the urine is added a sufficient quantity of hydrochloric acid to render it strongly acid—if the hydrochloric acid is not available nitric may be used but is not so good as it tends to oxidise the indican to a yellow compound called isatin. To the acid urine is added about one-eighth its volume of chloroform. It is then well shaken so that the air is thoroughly mixed with it. If indican is present in great amount the chloroform as it sinks to the bottom of the test tube (or bottle—the reaction can be well done in an eight-ounce bottle) will be coloured a blue or purplish blue. If it remains colourless potassium permanganate is slowly added with frequent shakings until a blue colour develops. If this is very intense and appears soon the indican is in excess of the normal. If it does not appear at all it is very improbable that there is much intestinal putrefaction.

Meat may be given and anything else that the patient has a fancy for so long as it fulfills the requisities of being easily assimilable and of comparatively small bulk. Highly seasoned foods should be avoided.

The permissible variations of diet can be worked out if it be remembered that the gastric and intestinal juices are deficient and that intestinal putrefaction is a source of danger.

Drugs.—Of these arsenic is the most important and it may be given in several ways—for each of these advantages are claimed by various authors. Arsenic given by the mouth is best and most conveniently given as the Liq. Arsenicalis Hydrochlor. or Fowler's solution. Beginning with small doses it is worked up to the limits of toleration which differ with different patients. Signs of arsenical poisoning are loss of the knee jerks, pigmentation, neuritis, desquamation and discolouration of the skin and even thickening of the epidermis on the palms of the hands and soles of the feet. The loss of knee jerks is one of the earliest to appear but it is to be borne in mind that it may also be due to nervous lesions which are part of the disease for which arsenic has been given.

Arsenic may also be given hypodermically (see page 347) and intravenously as salvarsan. It is extremely doubtful whether these measures have any advantage over administration by the mouth but as arsenic has in vitro some action in the direction of rendering the red cells less liable to hæmolyse there are theoretical reasons in favour of intravenous injection. These are somewhat vitiated by the reflection that if the arsenic happened to be in too strong concentration it would probably cause hæmolysis instead of preventing it.

For details of arsenic administration see page 347.

Iron is of little value in the acute stage and may even do harm but when the patient is convalescent it may be usefully employed to restore the blood to normal if possible before the onset of a relapse.

It may be given in the various forms mentioned on page 355, and should be combined with arsenic.

Other drugs are of use only for the purpose of combating heart failure, vomiting, etc. Digitalis is useful in the former case and alcohol is often of value in small doses. This may not accord with the advertised pharmacology of the latter drug but experience seems to warrant its use.

Vomiting may be a very troublesome complication and unfortunately there is no drug specific for this complication. Attention is more profitably directed to gastric lavage, regulation of the diet, and complete rest than to drug administration. Vomiting does not afford an indication for the discontinuance of arsenic but if that seems well to the physician—or patient—subcutaneous administration may be used as an alternative. Bismuth is as a rule useless and if tried may be best given in the form of Elixir Bismuthi Salicylatis—the dose being 1/2 drachm three times a day. This is an excellent preparation.

For transfusion see Chapter XXII, where the indications for it are discussed and the precautions necessary.

For hæmorrhage and its treatment see Chapter XXII.

Complications other than those mentioned are to be met with the same treatment as would be applicable in any other disease.

OTHER HÆMOLYTIC ANÆMIAS

These are dealt with under secondary anæmias with which they have many clinical affinities (page 191).

CHAPTER XIII

HÆMOCHROMATOSIS, HÆMATOPORPHYRINURIA, HÆMOGLOBINURIA, ETC.

HÆMOCHROMATOSIS

Synonyms.—Bronzed diabetes.

Definition.—A disorder of blood destruction leading to pigmentation of the skin and sometimes of other organs, cirrhosis of the liver and glycosuria.

Nature.—It is probable that the disorder of blood destruction is primary but the cause of it is quite unknown.

General Pathology.—We are obliged to hypothecate some disorder of blood destruction because the pigment which is found contains iron and there seems no other possible source for it. At the same time there is no definite evidence of increased blood destruction nor that it is, on the other hand, diminished. We cannot thus go further than to say that it is disordered.

The deposit of the pigment in the skin leads to the first of the clinical manifestations, *i.e.*, a brownish colouration. The deposit of the same in the liver leads to destruction of the cells and fibrosis and the deposit in the pancreas leads to glycosuria. Thus the three chief clinical features arise. Finally the patient dies—commonly of coma but sometimes of intercurrent disease.

Etiology.—The only etiological factor which seems to have been at all frequently present is alcoholism and this is not sufficiently in evidence to enable us to lay much emphasis on it except as a contributory factor.

Age and Sex.—The disease seldom shows itself before the fourth decade or after the sixth. It is almost wholly confined to men, only one or two cases having been met with in women.

Onset.—Often the apparent onset is rather sudden but the actual commencement of the disease is gradual in most cases. Thus weakness, thirst, pain over the liver, etc., are commonly complained of and these are only likely to occur when the disease is well established.

General Symptomatology.—This combines the symptoms of cirrhosis with those of diabetes and any full account of the various clinical manifestations to which these may give rise is unnecessary. Only a few symptoms require separate mention.

The Blood.—Except for the occasional presence of a more or less obvious lipæmia there is little to note. There is not infrequently a slight grade of polycythæmia and any severe anæmia is not to be expected. (See page 365 for the blood changes in diabetes.)

Spleen.—This is often slightly enlarged. The lymphatic glands are not enlarged.

Liver.—This enlarges progressively. When examined post mortem it is found to be of the hob-nail variety and of a deep brownish-red colour.

Pancreas.—Similar changes are found in the pancreas.

Urine.—This is sometimes of a rather unusually dark colour but is not found to contain bile unless the cirrhosis is advanced. Nor does it contain excess of urobilin.

The amount of sugar varies but is typically large rather than small. The sugar present answers the ordinary tests for glucose.

Skin and Mucous Membrane.—The pigmentation of the skin is most intense on the face and hands, less often well marked on the genitals and often almost absent on the rest of the body. It may, however, be very widely distributed.

The colour varies from a light brown in slight or early cases to a very typical slate colour—the latter is almost impossible to define but is not unlike the colour of a prominent vein seen through the skin with a slight admixture of red seen in the capillaries.

Other skin manifestations are not common with the exception of jaundice which further complicates the colour scheme. Purpura has been recorded.

The visible mucous membranes are not pigmented.

Course.—This is progressive except in so far as diabetic symptoms may be modified by treatment and so produce a transitory improvement.

Duration.—This is indefinite but after the onset of glycosuria is seldom more than a year.

Diagnosis.—This must be made from the triad of symptoms, pigmentation, cirrhosis of the liver and glycosuria. If there is any doubt a piece of skin should be examined microscopically. If an iron-containing pigment is found in the cells of the sweat glands the disease is hæmochromatosis. If it is not there present the disease is probably of different origin.

Treatment.—This, unfortunately, is purely symptomatic.

HÆMATOPORPHYRINURIA

Definition.—The presence in the urine of various abnormal colouring matters including excess of hæmatoporphyrin.

Nature.—This is a disorder of metabolism and very probably of hepatic metabolism. It is not known to depend on bacterial action but is known to follow the use of certain drugs. The cases in which drug taking could be eliminated have sometimes shewn marked signs of intestinal disorder but others have been in apparently normal health.

General Pathology.—Of this almost nothing is known. The abnormal pigments in the urine are derived from the blood and their excretion is not confined to the kidneys but also takes place through the intestine. There is no evidence of excess of blood destruction so that we are obliged to suppose that the normal process of blood destruction is disordered. Hæmatoporphyrin itself is iron free and so is a relatively late product of katabolism of the blood pigment hæmoglobin, but the nature of the accompanying pigments—which are largely responsible in many cases for the deep colour of the urine—is uncertain.

Etiology.—The great majority of cases have followed the administration of sulphonal, trional or tetronal but there remain a few idiopathic cases and it is these which are of chief importance from the point of view of this volume. They have been met with chiefly in males, although not to the overwhelming extent that was noted in hæmochromatosis. In a few cases there was a possibility that intestinal stasis was an etiological factor. It is, however, to be remembered that it may be a symptom only, in sulphonal poisoning it is hardly ever absent. Two cases have been noted in the same house with no apparent connecting link other than the same place of residence. It is noteworthy that one of these occurred in a woman who had proved very susceptible to one of the coal-tar derivatives, all of which are apt to cause intra-vascular hæmolysis. The age of onset is very variable and there is not enough evidence to suggest at what age it is likely to be most commonly met with.

A familial tendency has been more than once noted and in one such case two brothers were affected with hæmatoporphyrinuria of paroxysmal occurrence and accompanied by a bullous skin eruption—hydroa æstivale.

It is thus obvious that our knowledge of the etiology is very slight and lacks co-ordination nor is it likely to be improved until more cases are recorded.

Onset.—This is commonly sudden, *i.e.*, the pigment is noticed in the urine in large amount without any warning. When there are any symptoms these accompany the appearance of the hæmatoporphyrinuria.

Symptoms.—The toxic symptoms when present consist of constipation and distention of the abdomen. This may proceed to absolute obstruction and death. The usual accompanying symptoms may be present and very severe. On the other hand gradual recovery may ensue. The rare presence of hydroa æstivale has already been mentioned.

Otherwise the symptoms have been only those of concurrent diseases and these have been so various in nature that no good purpose would be served by detailing them under a description of the symptoms of hæmatoporphyrinuria.

The condition of the urine is dealt with below.

Blood.—There is nothing in this which seems to have any direct bearing on the problem of its disordered destruction—which is further evidence that the disease is a true disorder of blood destruction and is not in any way affected by the composition of the blood itself. At the same time this is just one of those points on which it would be very unwise to dogmatise in the present inadequate state of our knowledge.

A leucocytosis may be present in toxic cases.

Spleen.—This is not enlarged.

Liver.—Certain changes of degenerative nature have been noted in the liver after death but these have not been constant and their significance is very uncertain.

Urine.—The amount of the urine does not seem to be disturbed as is the case in hæmoglobinuria and for all practical purposes the abnormal pigments alone require consideration.

The colour to the naked eye varies within wide limits. The lightest tint often resembles that seen in hæmaturia, *i.e.*, is almost blood red, but the urine is nevertheless not so opaque as would be the case if blood were present. The darkest tint is almost black. Hæmatoporphyrin itself has not very intense colouring properties and it is chiefly the other and unidentified pigments which produce this range of colour and also the depth of colouration.

Hæmatoporphyrin cannot be identified without the aid of the spectroscope. The characteristic spectrum can be seen in most cases in the urine as it is passed, but extraction of the pigment may rarely be necessary. In this case the urine is rendered strongly alkaline with ammonia or potash and barium chloride added. This produces a copious precipitate which, in turn, carries down the hæmatoporphyrin. The precipitate is collected on a filter paper and extracted by washing with hot alcohol. The resulting solution gives the spectrum shewn in Fig. 37, page 284.

The other pigments do not give any spectroscopic bands and may or may not be carried down with the hæmatoporphyrin. They are not of diagnostic importance in consequence.

Course.—This is so variable that no average can be drawn. The symptom is seldom of fatal significance and the only deaths due to the disease seem to have been in those cases in which there was intense intestinal disorder as well. How far the symptom is at fault or how far death and the symptom are alike referable to some disorder to which we have no other clue, is unknown. Generally speaking the symptom is not associated with any fatal tendency.

Diagnosis.—This can only be made from the urinary examination and the identification of hæmatoporphyrin.

Treatment.—There is none directed to the hæmatoporphyrinuria and treatment of associated disorders is symptomatic.

HÆMOGLOBINURIA

Synonyms.—Paroxysmal hæmoglobinuria, icteric hæmoglobinuria, hæmaturia, hæmatinuria, methæmoglobinuria, paroxysmal methæmoglobinuria.

Definition.—A group of disorders characterised by the presence in the urine of hæmoglobin or of methæmoglobin freed from red cells.

Nature.—The condition is due to liberation of hæmoglobin from the circulating red cells, but it is not known whether this is due to external conditions primarily or to an altered state of the plasma or to some defect in the corpuscles. It is probable that in some cases one and in some another of these factors is the more important. Of course in a few cases the exact etiology is not in doubt, *e.g.*, after injection of ether into a vein, and we may then say that the nature of the disease is "toxic," but generally speaking there is no sufficient information available for defining the nature of this disorder apart from a catalogue of possible etiological factors.

General Pathology.—There is frequently a predisposing abnormal state of either the plasma or the red cells if we may make such a deduction from the common history of antecedent syphilis, the rare family incidence, etc.

It would appear that there must then be an exciting cause before an attack takes place—in some cases when hæmoglobinuria is a transitory and non-recurrent disorder, predisposing and exciting cause are the same. Of the exciting causes in the paroxysmal cases cold is that most frequently mentioned.

Cold constricts the vessels of exposed parts and tends to inspissate the blood therein. At the same time there is probably vasodilatation in deeper parts. One or other of these factors (the first is commonly incriminated) determines the break-up of red cells in the circulation and deficiencies in rouleaux formation, etc., bear witness to this adverse effect on the red cells. Hæmoglobin is liberated and may in some cases be detected in the plasma. In any case it finds its way to the urine via the kidneys and this very speedily. In the urine it may be converted into methæmoglobin but this is really an unessential part of the disorder as it takes place outside the body, *i.e.*, external to the tissues.

The exciting cause ceasing to act, the hæmoglobinuria is no more seen.

There are other factors in the pathology which have not been mentioned but which are nevertheless common. The hæmoglobin is not always liberated only by the urine. Some of it may be eliminated through the liver and a hæmatogenous jaundice may ensue with tenderness of the liver clinically. Again the share which the spleen must take in disposing of the red cells as apart from their hæmoglobin may lead to tenderness of that organ. In some cases it would appear that all the hæmoglobin is eliminated through the normal channel, *i.e.*, the liver, but albumen appears in the urine as the sole urinary sign of an attack.

There are also symptoms, such as fever, more difficult of explanation on a pathological basis and there remains the secondary anæmia which is a natural consequence of an attack.

These are dealt with more fully later.

Allied Diseases.—Hæmoglobinuria as a symptom or in its more or less definite form of paroxysmal hæmoglobinuria presents interesting analogies to many other diseases. Inasmuch as there is excessive blood destruction and some of the products may be excreted by the liver with accompanying jaundice it approaches cholæmia and other diseases in which there is an hæmatogenous jaundice. From these it is chiefly distinguished by the excretion in the urine not of pigment much altered but of the unaltered hæmoglobin. On what essential factor this difference depends it is impossible to do more than surmise.

Then there are three diseases which seem to bear a close relation to each other, viz., malaria, blackwater fever and hæmoglobinuria. Of the latter two malaria is commonly supposed to be a casually related antecedent. Hæmoglobinuria is sometimes met with in malaria as an unimportant but significant symptom. Moreover certain clinical symptoms, *e.g.*, shivering, tenderness of the spleen, fever, etc., may be met with in any of the three. Thus a malarial patient frequently shivers and is febrile without having hæmoglobinuria and one cannot say on what exactly this shivering depends. Similarly a hæmoglobinuric patient often has rigors and a high temperature without suspicion of malaria. There is thus, as is usually the case where the blood diseases are under discussion, ample scope for enquiry but little definite information.

With Raynaud's disease hæmoglobinuria has closer associations, for the two syndromes are often met with together or one may be found as an occasional complication of the other. Raynaud's disease is commonly spoken of as a vaso-motor neurosis, a term which indicates an attitude of mind on the part of the observer rather than a supported statement of its pathology. Yet if we are to bring hæmoglobinuria into line with the vaso-motor neuroses we must suppose that the disorder, in its paroxysmal form, is primarily dependent on an instability of the nervous system leading to over-contraction of the vessels from slight causes while the actual destruction of the red cells is entirely secondary to this or, alternatively, we may suppose that there is some general trophic disturbance of nutrition which in some way lowers the vitality of red cells. Either of these views has a good deal to recommend it but it will be seen that at present pursuit of the analogy between Raynaud's disease and hæmoglobinuria leaves us very much where we started.

The last analogy which need be mentioned is with the other diseases here grouped with hæmoglobinuria, viz., hæmochromatosis and hæmatoporphyrinuria. Of the first we know practically nothing; the second is occasionally of family incidence and of quite obscure causation but is usually frankly "toxic" and due to the administration of sulphonal. On the whole the proved analogies with hæmoglobinuria are of small importance and the three disorders are grouped together because they have this in common that they are little understood disorders of blood destruction.

Etiology.—*Of hæmoglobinuria as an occasional symptom;* it may occur in almost any of the specific fevers, *e.g.*, scarlet fever, pneumonia, etc., but is distinctly rare. It may also follow acute nephritis and, possibly, precede it. The exact connection is doubtful. It may be noted that the toxins elaborated during the course of any fever are blood destroying so far as can be gathered by examination of the blood so that an occasional excessive destruction leading to hæmoglobinuria is not surprising.

It may also follow exposure to excessive heat or excessive cold, but much more frequently—if one may use the term in connection with a rare disease—after exposure to cold.

Certain agents which disintegrate the red cells in the circulation produce hæmoglobinuria—although not invariably since the extent, etc., of destruction depends in part on the concentration of the poison or on similar variable factors. Of these the plasmodium of malaria is the best-known agent. This is a living agent but simple chemical agents may produce the same results. These are, however, seldom if ever in operation without the possibility of hæmoglobinuria being borne in mind so that difficulty does not arise. One may instance the recent practice of intravenous injection of ether solution as a cause of hæmoglobinuria of a purely chemical nature although owing to the low percentage of ether in the solution administered the symptom does not often occur in practice.

(The remainder of this section is to be taken as referring to paroxysmal hæmoglobinuria alone.)

Of paroxysmal hæmoglobinuria; predisposing: This is not at all commonly a familial disease but it may be borne in mind that it has been reported in such a form. On the other hand the sporadic cases are perhaps more often encountered where there is an insane or at least neurotic heredity and especially where this is connected with a syphilitic taint. Malaria was formerly invoked as a strong predisposing factor but cannot be so regarded. Malaria may certainly be accompanied by hæmoglobinuria and even by a recurrent form since malaria itself is recurrent but this does not suffice to identify it with the clinical entity now to be described. Moreover malaria is a disease of warm climates which paroxysmal hæmoglobinuria is certainly not and malaria is no respecter of sex while paroxysmal hæmoglobinuria has a distinct partiality.

Hereditary syphilis has already been mentioned and is chiefly seen in the younger and rarer cases, in a large percentage of older cases there is an undoubted history of acquired syphilis exceeding the percentage of cases of syphilis in the classes from which these cases are drawn.

Exciting.—Of these cold is the most frequently in operation and apparently the most potent. Not only does exposure to intense cold produce hæmoglobinuria in a predisposed person but exposure to relatively small variations in temperature. Moreover, exposure of a small area, *e.g.*, one finger, to the cold of an iced fluid may bring on an attack, in fact, may be expected to bring on an attack. It is not apparently material whether it be a "dry" or a "moist" cold so long as there is a variation in temperature. As exemplifying the trivial nature of the exciting cause in some cases it may be mentioned that in one case the mere laying of the hand on cold metal or marble was sufficient to induce a paroxysm.

In some cases unusual exertion may lead to a paroxysm and in others it would appear that mental excitement or stress may have the same effect. These are, however, the rarer class of case and alteration in temperature must be regarded as the typical exciting factor.

Age and Sex.—As a rule paroxysmal hæmoglobinuria is a disorder of the second and third decades but may occur at any age from soon after birth to seventy or more.

It is predominantly a disease of the male sex although sufficient authentic cases in females are on record to make it appear that they are by no means exempt. This partiality for the male sex is shared by the majority of the diseases dealt with in this volume. This fact invites some general theory to fit the case and one may surmise that just as the muscles of the male sex are more highly developed for the proper functions of that sex so are the blood-forming organs of the female sex less liable to disease that they may more adequately perform the special duty of nourishing the fœtus. It is interesting that almost the only blood disease in which the female sex is most affected, viz., chlorosis, is one in which the blood, so far from being weakened, is in distinct quantitative and qualitative excess (see page 306).

Onset.—The first paroxysm of the disease commonly follows some severe exposure, greater than would be required subsequently. The first symptoms are general and severe malaise with shivering or a distinct rigor. These are of sudden appearance.

General Symptomatology.—There is first a feeling of cold with shivering and perhaps local or slight general cyanosis. This is accompanied by headache, often by pain in the back and loins and very frequently by a feeling of numbness in the legs and feet. The temperature rises rather rapidly and within a short time of the attack of shivering the patient passes a certain amount of very dark urine. He may at the same time become slightly but distinctly jaundiced. With the passage of the blood in the urine the malaise vanishes to some extent but persistent and unusual malaise may exist between the attacks if the intervals are small.

This may be taken as a typical attack but there may be many more symptoms and the attack may be much more protracted. In general an attack is over in three to five hours in a typical case.

Fever.—This is usual but some cases show no rise of temperature. It rises in a typical case during the paroxysm to 102 or 103° F. and falls rapidly when the paroxysm is over. Temperatures of 105° F. and over have been recorded but are exceptional.

Nervous System.—The not infrequent instability of the nervous system has been referred to already in so far as neuropathic heredity is concerned. There are very many symptoms which may be connected with the nervous system yet to be mentioned.

Such organic diseases as are connected with syphilis of the nervous system may be met with but otherwise organic nervous disease does not occur other than as an accidental complication.

Pain is a feature of the attacks and is of various sorts. Pain in the lumbar region of a dull "lumbago" character is quite common and in the kidney region there may be very acute shooting pain. Headache is common and may be severe. The pain in the limbs is more that of weariness or heaviness than real pain—should, in fact, be classed as a variety of paræsthesia. It is not usual to meet with painful micturition nor the referred pain of stone in the kidney or bladder.

Paræsthesia takes the form of numbness of the feet and legs; sometimes also of the trunk and upper extremities. Tactile sensation may be diminished at the time and even motor control impaired.

More especially if there be frequent attacks the patient is liable to a persistent malaise that goes far to incapacitate him from work of any sort. This depends in part on the anæmia but not wholly.

Signs of angio-neurosis are met with in the form of urticaria, Raynaud's syndrome, etc. The lesser degrees of "dead fingers" and increased susceptibility to cold (otherwise than as tending to produce hæmoglobinuria) are relatively more common.

Circulatory System.—This is not particularly affected except in so far as it is involved in Raynaud's syndrome and similar affections incidental to the disease. These have already been mentioned.

Blood.—This shews a secondary anæmia of the type seen after hæmorrhage, *i.e.*, accompanied by a leucocytosis, but if much of the liberated hæmoglobin has been eliminated otherwise than by the kidneys and in a changed state, there may be the so-called "pernicious" type. In the latter case there may be many nucleated red cells, megalocytes, etc.

Hæmoglobin may sometimes be detected free in the serum if the blood be examined at the right moment but the right moment can only be ascertained by a series of blood examinations undertaken at least hourly from the commencement of an attack. If a little of the blood be allowed to stand in a capsule, the cells will separate out leaving the clear serum around the clot. If this serum is tinged with red, hæmoglobin may be understood to be present free in the serum. It is even better to centrifugalise a small tube of blood but much care must be taken to see that the blood is not heated or otherwise injured.

There is not infrequently a curious lack of the normal rouleaux formation and this can be estimated by examining a living film, *i.e.*, a drop of fresh blood on a slide, fresh and covered with a clean cover slip. This is not seen between attacks.

Spleen.—This is not uncommonly enlarged—especially after a severe attack—but is not more than comfortably palpable at the most. It may be tender to palpation. The enlargement subsides between attacks.

Lymph Glands.—These are not affected but the hæmolymph glands are probably enlarged, albeit this point is not established.

Urogenital System.—Occasionally some mild degree of nephritis has been noted but not sufficient to lend any support to the view that kidney lesions are primary. There are not even signs of any particular damage to the kidneys in most cases in which this point is examinable. During an acute attack it might be expected that the kidneys would be enlarged and the tubules more or less blocked with hæmoglobin. This is probably the case but as patients do not as a rule die in attacks, it is difficult to say. Support to the view that there must exist very considerable congestion of the kidneys at the time of attacks is derived from the existence of pain in the kidney region—which is common.

Urine.—There is commonly frequency of micturition during a paroxysm but this does not mean that a very undue amount is passed. During the paroxysm the amount passed is less than normal and only after the paroxysm does the total amount rise considerably.

Blood appears in the urine about an hour after the onset of shivering and persists for a few hours—seldom as much as ten.

Red corpuscles are few in number if present at all. Urea is usually increased and oxalates are very often present in excess. Albuminuria is a feature of the disease and may be present when there is no hæmoglobinuria.

Bile is sometimes present in the urine after very severe paroxysms.

Obviously the colour of the urine will vary considerably in different cases and at different times during the course of an individual paroxysm. If methæmoglobin is formed the urine will have a more brownish tinge.

The essential diagnostic point about the urine is that it contains a very large amount of hæmoglobin and a very few or no red cells. Thus a microscopical examination should not be omitted if the diagnosis is to be rendered secure. At the same time in a case in which the clinical features are paroxysmal and recurrent as already mentioned even a red-coloured urine without more detailed examination would tend to clinch the diagnosis.

Skin.—The colour of the skin is only modified by the presence of jaundice, that is, taking the skin as a whole but there are certain localised affections. Of these urticaria is the most striking and is not very infrequent. It may affect any part and has a certain partiality for the face—it is apt to be of the giant form rather than on a lesser scale.

Purpura has been recorded but is uncommon. Either purpura or urticaria may be expected to vanish as the attack passes off but they may also herald an attack.

Course and Duration.—The course is very irregular. There may be two attacks in one day which is rare or there may be so long an interval as a year between attacks. Every variety of interval between these two extremes may be met with. An individual case will probably know at what intervals attacks may be expected, provided he takes the ordinary risks of life with regard to exposure to cold, etc., but he will also know that he can never be quite certain when the next attack will occur.

The duration of the disease is indefinite. There seems to be no lethal tendency and patients commonly die of some unrelated intercurrent disease. If the attacks are very frequent the anæmia may be a danger.

Diagnosis.—This rests on the detection of hæmoglobinuria (see above) occurring in a paroxysmal form. If this occurs in any instance the symptom complex—paroxysmal hæmoglobinuria—is present and the diagnosis is made.

Treatment.—Where there is an obvious pre-existing and possibly predisposing disease that should be treated. Thus excellent results have been obtained by the use of antisyphilitic treatment in some cases. The hæmoglobinuria has entirely disappeared.

Since cold is an exciting factor and less commonly exercise (particularly long walks) the attacks will be less frequent in so far as these are avoided. Cold may be avoided by residence in a warm climate—sometimes with complete success. On returning to a cold climate attacks again appear.

Various drugs have been recommended including arsenic and hæmostatics such as calcium chloride. Neither of these would appear to be at all specific and preventive measures are undoubtedly the most efficacious.

During the attacks warmth in every available form should be applied internally and externally. As in black-water fever, a large amount of fluid should be given in order to counteract any undue concentration of hæmoglobin in the kidneys, although, as already mentioned, this never seems to have caused any permanent damage of note.

INTRAVASCULAR CYTOPHAGOCYTOSIS

This condition is also known as auto-erythro-phagocytosis and as phagocytic anæmia. It is very rare and a discussion of its etiology would be out of place here. It is characterized by active phagocytosis of blood cells by other blood cells of normal or abnormal type actually in the circulating blood. The resulting blood picture is very striking. In one case the phagocytosis was so pronounced that it was calculated that if all the cells were as actively phagocytic as one which was observed actually engulphing cells on the warm stage the whole of the red cells of the body would have been destroyed in less than two hours. In this case the destruction produced a fatal anæmia. Other cases have followed transfusion or been associated with some known hæmolytic process such as cholæmia. Isolated phagocytic cells may be met with in malaria and leukæmia and no doubt in other diseases. Although all cells of the white series have been seen active in some cases there is usually added a cell not found as a rule in the blood but of normal occurrence in the spleen and probably in the hæmolymph glands. This is a cell with a single or multiple nuclei and appears to be of endothelial origin. In the earliest case of which the author can find record the spleen had been removed surgically some time before the intravascular cytophagocytosis was noticed. It is therefore apparent that there are many points requiring settlement with regard to this blood symptom (it is not a disease per se) and when such cases are met with they ought to be carefully recorded. Although references have been as a rule excluded from this volume one is given to the best paper on the subject and any one inclined to dogmatise about the limits of hæmocytology ought first to read the article in question.[1]

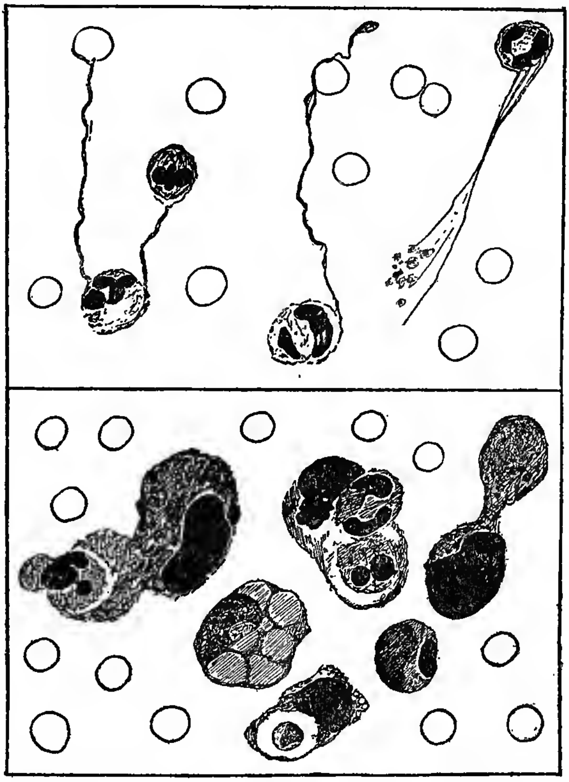


FIG. 35.—A drawing of the cells in various of the reported cases of intravascular cytophagocytosis. The upper part shows polymorphs with long processes which are attaching themselves to other cells. The latter are drawn up into the phagocyte and ingested. The lower part shows large mononuclear phagocytes, many of them containing several cells or portions of cells which have been caught. Drawn by the author from photographs.

---

[1] Mary Rowley: Journ. of Exp. Med., x, 1908, pp. 78–97.

CHAPTER XIV

PARASITIC DISEASES OF THE CIRCULATING RED CELLS

There are many members of this group already and new ones are being discovered with considerable frequency. Malaria is the chief but there is good reason to suppose that the intra-corpuscular parasites described in other tropical diseases, especially in the more obscure insect-borne fevers, will presently be accepted as the real causes of those diseases. There are also a great number of diseases in which there are parasites in the blood although they may not primarily affect the red cells.

It will thus be apparent that to endeavour to deal adequately with the parasitic diseases of the blood would be to enlarge the scope of this book to an unwarrantable extent.

The reader is therefore referred to text-books of tropical medicine for details of the nature, forms, etc., of the parasites while the changes in the blood cells of a secondary nature will be briefly referred to under Various Diseases (page 356).

CHAPTER XV

CYANOSIS

As cyanosis is a not infrequent accompaniment of some blood diseases and is in itself an abnormality of the blood it will, perhaps, be well to give somewhat detailed consideration to its etiology and nature.

If the blood be driven out of some portion of a cyanosed surface such as the skin, it will be seen that the bluish colour vanishes at the same time. The blue colour, then, is a property of the blood. In health this colour is only seen in venous blood as may be demonstrated by pressure against the flow along any large superficial vein. The colour is thus abolished and the course of the vein no longer apparent. The difference between venous and arterial blood is that the latter contains more oxygen in combination with its hæmoglobin. The resulting compound is called oxy-hæmoglobin and it becomes reduced to hæmoglobin by its passage among the tissues which remove from it the oxygen which is essential for the proper performance of their functions. Hæmoglobin is of a distinctly more blue colour than oxy-hæmoglobin and the venous blood is accordingly darker in hue. Even venous blood, however, contains a considerable amount of unreduced oxy-hæmoglobin but if it remains longer than is usual in contact with the tissues this also may be reduced and intense cyanosis results. On the other hand, although the blood may circulate at the normal rate there may be an insufficient supply of oxygen available and the hæmoglobin will in this case not be re-oxygenated and again cyanosis will result. These are the two ways in which cyanosis is most often produced. It is also apparent in the presence of certain abnormal compounds of hæmoglobin which will be subsequently dealt with.

All cases of cyanosis can therefore be brought into one of the following classes, in which there is present one of the three conditions, viz.:

1. Stagnation in the capillaries.
2. Deficient oxygenation.
3. Abnormal compounds of hæmoglobin.

The first two are apt to co-exist, as stagnation in the capillaries of the lung will naturally result in deficient oxygenation and on the other hand deficient oxygenation leads to physiological increase in the number of corpuscles, and to increased viscosity of the blood, and therefore to some measure of stagnation. Abnormal compounds result from intestinal disorders, so broadly speaking we can say of the three classes that in the first the circulatory apparatus is at fault, in the second the lungs are not doing their work adequately and in the third the digestive system is disordered. Cases of deep cyanosis are usually readily referred to the right class but when the cyanosis is slight there may be real difficulty in deciding what the condition results from. The chief etiological factors will therefore be considered in more detail.

The most important causes of stagnation in the capillaries are:

a. Deficient vis a tergo. This is the deciding factor in the cyanosis which occurs toward the end in cases of heart, particularly mitral, disease. It may occur, also, in pericarditis, etc.

b. Constriction of arterioles. This may be due to exposure to cold, vaso-motor disturbance or neurosis and to disease of the vessels. The latter, however, comes on slowly and the heart adjusts itself to the altered conditions and moreover the capillaries are not themselves involved in the disease.

c. Obstruction to the flow of blood. This is the case in thrombosis of or pressure on large vessels, particularly veins. The cyanosis is usually local.

d. Complete occlusion of vessels. This is also a cause of local cyanosis. It is imitated by the surgeon by the application of a tourniquet and in the treatment by congestion initiated by Bier. In the first case the limb is first emptied of blood and although what is left changes colour there is not always enough to give rise to visible cyanosis. In the second case the

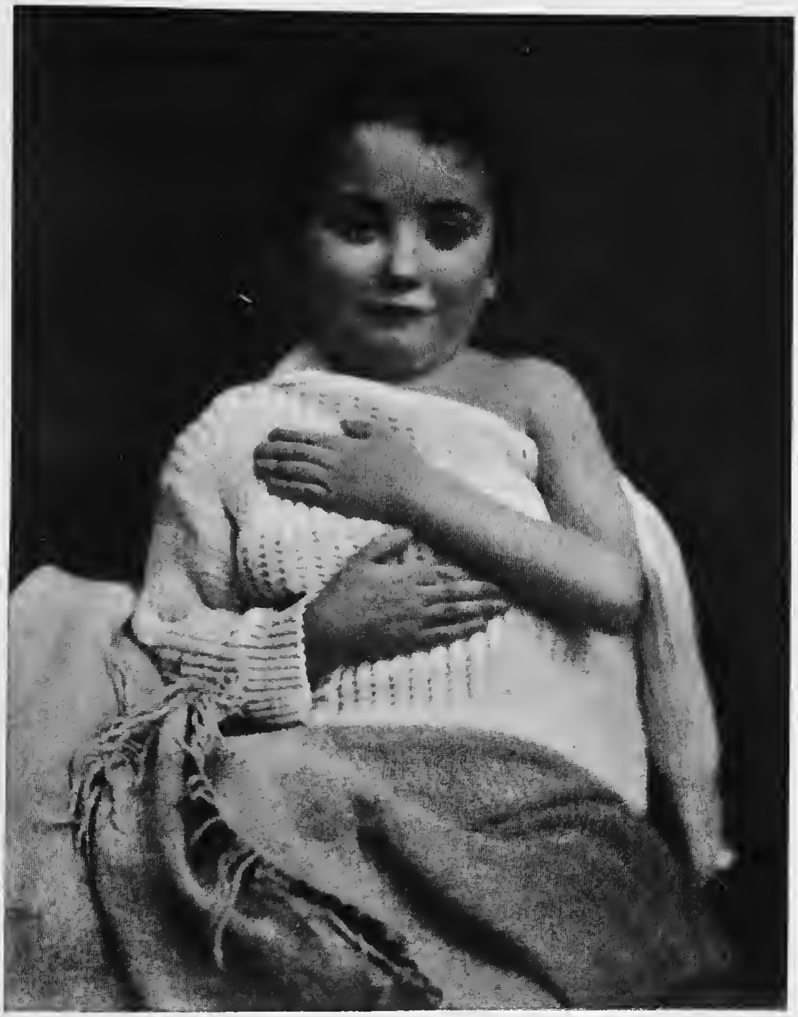


FIG. 36.—Cyanosis in congenital heart disease.

treatment is not properly carried out unless there is a visible tinge of blue and the veins only are occluded—and not all of these. It really falls in the previous class but is introduced here to contrast with the tourniquet.

e. Increased volume of the blood. This by itself cannot cause sufficient stagnation to produce cyanosis but it is a contributory cause in a few cases, *e.g.*, in erythræmia and probably in the plethora seen in those who lived not wisely but very much too well.

f. Increased concentration of the blood. This causes stagnation by first producing increased viscosity. It is operative in diseases accompanied with great loss of fluid, *e.g.*, cholera, in many cases of shock and exposure and in all cases where deficient oxygenation has caused a polycythæmia or increase in the number of red corpuscles per c.m.m. It is the chief cause of the cyanosis of erythræmia.

Deficient oxygenation of the blood occurs, as has been noted, chiefly when the lung is at fault. There are four ways in which it may be caused.

g. Failure of venous blood to reach the lungs. This is seen in some cases of congenital heart disease but very rarely in any other condition. The blood may be, as it were, short-circuited through a patent foramen ovale and so fail to reach the lungs. Only a part of the whole volume of the blood is so disposed of and even when the anatomical conditions make it possible for the admixture to occur this amount may not be sufficient to produce visible cyanosis.

h. Obstructed flow of blood in the pulmonary circulation. This, unless it is thoroughly compensated which is seldom the case, means that there is not sufficient blood passed through the lungs per unit of time to allow of the presence of the requisite amount of oxy-hæmoglobin in the general circulation. The tissues take up the oxygen more quickly than it can be replaced. It may be one of the results of pulmonary stenosis (usually congenital) or more rarely be due to pressure on the pulmonary vessels by tumours.

i. Deficiency of lung surface. This may be due to actual loss of lung tissue or to the involvement of the lung by disease.

The first is present in emphysema, a very common cause of cyanosis. Among the diseases which reduce the amount of surface available for the oxygenation of the blood are phthisis, pneumonia and abscess and those which produce collapse by pressure, *e.g.*, pleural effusion, mediastinal new growths and pneumo-thorax.

j. Deficient entry of oxygen. This may be due to vitiated atmospheres in which the amount of oxygen is below normal or to obstruction to the entry of air. In the latter class come among other diseases spasm of the glottis, impaction of foreign bodies, and pressure by growths and aneurysm.

Abnormal compounds of hæmoglobin are rare and fall into two classes according to the compound present.

k. Sulph-hæmoglobinæmia. This is described elsewhere in detail. The colour differs from that seen in other cases of cyanosis. It is rather a dull grey than a blue and is accompanied by intense pallor. It depends on intestinal disorders.

l. Met-hæmoglobinæmia. This compound again produces a different colour to that of the more common forms of cyanosis. It is rather a bright blue and resembles the last in the presence of intense pallor. It is usually caused by the taking of drugs, especially aniline derivatives, but in a few cases has seemed to depend on disorders of the digestive apparatus.

An analysis of some of the commoner examples of cyanosis will help to demonstrate the multiplicity of mutually reinforcing agencies which are at work in most cases. It is very important to remember that one cause seldom acts alone. Take, for instance, a case of congenital heart disease. The cyanosis may in the first place result from actual admixture of arterial and venous blood, the latter thus failing in part to reach the lung. The same malformation that causes this may be responsible for mechanical disadvantages sufficiently serious to seriously impair the efficiency of the vis a tergo. There may be also stenosis of the pulmonary arteries and this will mean that there is some stagnation in the capillaries. The blood to compensate for the deficient aeration will become more concentrated and this in turn will probably be associated with some increase in volume. Both of these will still further increase the stagnation.

It has also been suggested that in cases of congenital cyanosis there is a certain amount of fibrosis of the lung and this will reduce the surface over which the blood can come into contact with the inspired air. Although all these factors may not be in operation in one individual case it is apparent how they depend on each other in many respects and it also is apparent that the presence or absence of visible cyanosis in heart disease congenital in origin cannot always be ascribed to the presence or absence of any one factor. Emphysema is a familiar disease in which cyanosis is often seen. There is in the first place loss of lung tissue and it is also possible that this loss of tissue allows of some of the blood passing direct from the smaller arteries to the smaller veins. Both of these mean in effect diminished oxygenation. The same increased viscosity of the blood follows as in the last example. The stagnation and increased viscosity embarrass the heart and in the later stages the force of the vis a tergo is seriously impaired, in fact this is usually the cause of death when lung complications are absent.

Many other examples might be quoted but these suffice to show that in most cases associated with cyanosis the causes of its occurrence are many and are to some extent mutually dependent on each other.

CARBOXYHÆMOGLOBINÆMIA

Synonyms.—Coal-gas poisoning, carbon monoxide poisoning.

Definition.—A condition in which some of the oxygen normally combined with the hæmoglobin of the red corpuscles is replaced by carbon monoxide. It arises as an acute condition in mine disasters, etc.—whenever people are exposed to the fumes in question and a chronic poisoning is very rare.

Nature.—This is a toxæmia—that is to say, the whole disease is the presence of a toxic substance in the blood, to wit, carbon monoxide. Our medical phraseology is so perverted that the word "toxæmia" is becoming synonymous with either bacterial infection or the influence of some agent at present neither defined nor identified. Nevertheless facts remain and this is undisputably one of the best and purest examples of a toxæmia that one can require.

General Pathology.—The toxic action of CO depends on its combination with hæmoglobin from which it displaces the oxygen normally combined.

The symptoms and pathology depend to some extent on the percentage of CO in the inspired air. Very high percentages such as 90 per cent.–100 per cent. kill at once by deprivation of oxygen and such cases are deaths from asphyxia and not from CO poisoning proper. After death it may be impossible to detect any CO in their blood which shows that it was not

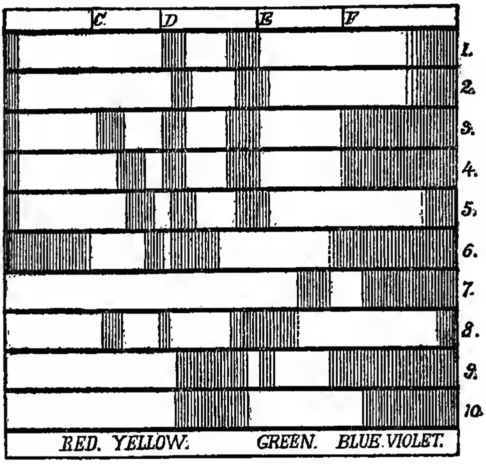


FIG. 37.—1. Oxy-hæmoglobin—normal spectrum of fresh blood. 2. Spectrum of CO-hæmoglobin. Prepared by passing coal gas through normal blood. 3. Spectrum of methæmoglobin. Found in the blood of some cases of "enterogenous cyanosis," in acute poisoning with various aniline derivatives and other drugs, and in the urine of hæmoglobinuria. On the addition of ammonium sulphide the spectrum changes to No. 10. 4. Spectrum of sulph-hæmoglobin. Found in the blood in some cases of "enterogenous cyanosis." It is not altered by the addition of small quantities of ammonium sulphide. 5. The characteristic change produced in the spectrum of sulph-hæmoglobin by passing through it coal gas. All the bands are shifted toward the blue end of the spectrum. 6. The spectrum of hæmatoporphyrin in acid solution. Found in the urine in sulphonal poisoning, etc. 7. The spectrum of urobilin. This is a product of the destruction in the body of red blood corpuscles—*i.e.*, of hæmolysis. It is found increased in the urine in many cases of pernicious anæmia, in cholæmia, etc. 8. The spectrum of acid hæmatin. Produced by the decomposition of blood in acid solution. It is important to demonstrate this spectrum when it is desired to ascertain whether a given substance is blood. 9. The spectrum of hæmochromogen or reduced hæmatin. Prepared by dissolving the suspected pigment in potassium hydrate and then adding ammonium sulphide. The spectrum is easily demonstrated and very characteristic. 10. The spectrum of hæmoglobin, sometimes called "reduced hæmoglobin." The colouring matter of blood deprived of oxygen; it exists in venous blood. Nos. 8 and 9 are important in medico-legal tests.

the formation of CO-hæmoglobin that killed them but the insufficient supply of oxygen such as is present in any atmosphere charged with a large volume of some other gas.

In a second class of case the symptoms of both asphyxia and of CO poisoning may be present and in these the percentage of CO must be conjectured to have suddenly increased. This might well happen in the case of the onward sweep of the after-damp following a mine explosion overtaking the escaping miners who had already been exposed to a small percentage of the CO and whose escape had perhaps been delayed thereby although it had not been sufficient to prove fatal before they were overtaken by the stronger gas.

In other cases the fatal termination is due to actual displacement of O by CO in combination with the hæmoglobin molecule. This takes place slowly but progressively in air so slightly contaminated that no unusual smell is noticed and more quickly according to the concentration of the CO in the air that is breathed. These are cases of uncomplicated CO poisoning.

The pathology of the disease is thus seen to be less simple than one might at first suppose to be the case.

Whatever be the percentage of CO in the atmosphere an animal exposed to it at once begins to absorb CO and in consequence to suffer from oxygen starvation. If, however, the percentage is extremely small the gas is eliminated as fast as it is taken up, if less small but still in by no means great quantity there is a period of half an hour or so before symptoms develop. As the blood is only exposed to the influence of the CO a little at a time this period is easily explicable. When the concentration reaches higher the symptoms commence. Meanwhile the percentage grows higher and higher and eventually the animal dies—before complete concentration is reached because the oxygen percentage has then fallen too low to support life.

If recovery takes place consequent on removal to fresh air, etc., the CO is slowly eliminated—in the course of about six hours it is no longer to be detected in the blood. It is slowly displaced by oxygen in spite of its greater affinity for hæmoglobin. Why this should be we do not know but it is none the less a fact that when the supply of CO is discontinued that already absorbed is slowly displaced by the oxygen of the air and much more quickly by pure oxygen.

Unfortunately deprivation of oxygen is not altogether compensated for by renewing the supply—there remain signs of deprivation in a weakened resistance of the tissues, etc

In a moderately acute case there may be a period, usually brief, of excitement when the inhalation of CO is commenced. The excitement quickly uses up the remaining oxygen and coma is consequently hastened. It is for this reason that rest is of importance in treatment and it also explains why people exposed to the fumes may keep conscious as long as they are sitting down but are suddenly overtaken by unconsciousness if they exert themselves to escape.

When there is no period of excitement, as is the fact in the majority of cases the nerve centres are slowly paralysed because it is impossible for them to carry on their functions without an adequate supply of oxygen. The higher centres suffer first, the respiratory and cardiac being the last to succumb. The fact that the heart fails last of all is of importance in treatment, for cessation of breathing is not necessarily a fatal sign if artificial respiration be immediately started.

Another result of the oxygen starvation is a fall of body temperature and this also is of importance in treatment as sudden exposure to cold air often produces collapse and even sudden death in those who otherwise should have recovered.

That the resistance of the tissues is diminished is shewn by the frequency with which patients die from pneumonia of the lobar type when they have recovered from the immediate effect of the gas.

In some cases—depending on some factor not sufficiently elucidated—the damage to the nervous centres is never recovered from and the patients may die after some days without recovering consciousness or may become permanently demented and die in an asylum.

General Symptomatology.—The onset of symptoms varies, as has already been mentioned, according to the percentage of the CO respired. The following account by a medical man, Dr. Le Neve Foster, is so striking that it is quoted somewhat fully from the official Report on the Snaefell Mining Disaster published in 1898. It is obvious that in this case the exertion of climbing brought the symptoms on more suddenly than would have otherwise been the case.

'The poison took effect most suddenly; probably its action was accelerated by the exertion of climbing rapidly. I felt decidedly queer when I reached the 115-fathom level, and thought a drop of brandy might revive me. I took out my little brandy flask; but already my fingers seemed incapable of doing the work properly, and someone unscrewed the stopper for me. I took a small sip and sat down. Everything then seemed in a whirl, and the atmosphere seemed a dense white fog. Sitting next to me were Captain R. and H.C.

'A curious fact is that we all sat without moving or trying to escape. The foot of the ladder was close by, yet none of us made an effort to go to it and ascend even a single rung. We none of us tried to walk a dozen steps, which would have led us to the other side of the shaft partition, where we all knew there was a current of better air. We simply sat on and on. Mr. W. remained motionless like a statue; Captain R. on the other hand was shouting and groaning nearly all the time, while H.C. was moving his arms. Of all this I was perfectly conscious although rooted to my seat . . . . . eventually, from long force of habit, I presume, I took out my note book. At what hour I first began to write I do not know for the few words written on the first page have no hour put to them. They were simply a few words of good-bye to my family badly scribbled . . . . . "I feel as if I were sleeping, no real pain, good-bye, good-bye, I feel as if I were dreaming. 2.15. We are all done. No (word illegible) or scarcely any, we are done, we are done, good-bye, my darlings."

'Among further notes occur the words:

'"No pain, it is merely like a dream, no pain, no pain, for the benefit of others I say no pain at all, no pain, no pain." I frequently wrote the same sentence over again . . . . . Mr. W. and Captain R., although not absolutely unconscious, did not recognise the lapse of time, for they thought only about ten minutes passed between my calling out "all up at once" and their arrival at the surface. In reality nearly two hours had gone by. That the numbness of my fingers recorded in my notes was no fancy was proved by the fact that I burnt my wrist and hand with the candle while sitting underground, and had no notion that I had done so until a friend in the evening called my attention to a big blister.'

The above extracts give a good idea of some, at least, of the symptoms that may be met with but they are, of course, chiefly those of a subjective nature. Amongst them we may note (1) a certain degree of excitement as evidenced by shouting, (2) apathy, as the failure to make any attempt to escape shows to have been present in all of the victims, (3) anæsthesia, (4) incoordination—the writing of the notes was bad, and (5) the modified state of the intellectual functions as witnessed by the inability to appreciate the passage of time.

All these have been noted in other cases and if it be borne in mind that some degree of excitement may first supervene and that the subsequent symptoms are those of paralysis of the nervous centres a scheme of the possible symptoms can be constructed—their name is legion.

Convulsions not very unlike those of strychnine poisoning may be met with as motor control is lost and these may be generalised or localised to one set of muscles such as those of the jaw. General relaxation and flaccidity of the extremities is more commonly met with and this may persist for some time.

Unconsciousness may be very profound and may last for several days; during this period there may be some recovery so that, for instance, electrical stimuli are resented by movement and by words. In spite of this a fatal termination may ensue.

Insanity when present is likely to take the form of dementia, mania is rare and brief.

It must be remembered that some of these symptoms and symptoms of paralysis of the motor as well as the mental functions may not be apparent at once, not indeed until some exertion precipitates their onset which might perhaps have been indefinitely delayed had the patient refrained from exercise.

The cerebral symptoms are rather apt to overshadow others but some of the latter are of considerable importance. Of these the state of the heart demands first attention. The pulse is increased in frequency and of poor quality being described as thready, poor tension, etc. Death from heart failure may easily occur after the patient has been removed from the influence of CO fumes. The temperature of the body is lowered during and for some time after exposure but there is in some cases a reaction later and the temperature may be elevated two or three degrees.

The lungs seem to be rendered especially vulnerable in CO-poisoning although the conjunctivæ also suffer and no mucous membrane is immune. Lobar pneumonia of the usual type is a frequent termination of the disease and the symptoms may not appear until the patient seems out of danger so that convalescence must be properly guarded at first.

The irritation of the air passages is also shewn by the frothy mucus which issues from the mouth in most acute cases.

There may be suppression of urine or, at least, partial suppression and in some cases there has been a trace of glycosuria.

Blood.—The blood is of a crimson or pink colour and according to the depth of the colour is the concentration of the CO in the blood. This may be estimated by the carmine method the principles of which are as follows:

Take three test tubes and in each place a measured amount of blood diluted to a known extent, *e.g.*, 100 times with water. In the first put the patient's blood, in the others normal blood. Prepare a weak solution of carmine of such a tint that it is about ten times as deep in tint as the diluted blood. The normal blood in one test tube is then to be saturated with CO by passing through it ordinary coal gas—the colour will change to a pink. This tube then contains saturated CO-hæmoglobin. The second tube is then treated with small amounts of carmine until its colour resembles that of the tube containing saturated CO-hæmoglobin. The amount of carmine solution necessary is then noted. Then X carmine solution is necessary to produce the tint of full CO saturation. A less amount will be necessary to produce the tint of full saturation in the tube containing the patient's blood, for it already contains a certain amount of CO. Carmine is therefore added to this tube until the requisite tint is obtained and the amount used noted. Then

The amount of carmine used in tube 1 : the amount of carmine used in tube 2 : : 100 per cent. saturation with CO : the previously unsaturated per cent. in the second tube.

The percentage not saturated being thus deduced the saturation of the patient's blood is obviously 100 per cent. less that amount.

There are no qualitative changes in the red corpuscles and any alteration in number will be due to concentration.

There is usually a leucocytosis in which the polymorphs predominate. It may amount to between twenty and thirty thousand per c.m.m.

The fluidity of the blood is not altered.

The CO-hæmoglobin is a stable body and it may be demonstrated months after death and even in the presence of general putrefaction.

Diagnosis.—This depends on the history of exposure to the gas which is usually clear enough but it must be remembered that a very small percentage of CO is sufficient to cause poisoning and that this may be derived from some source not in the patient's house, *e.g.*, a leak from the main outside. In one case the gas came into one room in a house and gave rise to symptoms which were not understood. The diagnosis was made and insisted on by a friend of the patient but was not approved by his medical advisers. The friend had her way and removed the patient, as it seemed on the point of death, to another house. He had revived so much on the way there that he was able to walk up the steps whereas he had been carried to the carriage at the other end. The sequel is even more interesting, for a gentleman who remained in the old house was that night for the first time affected by symptoms of poisoning. It seems that the first patient had been in the habit of keeping his room particularly warm and the gas seems to have been attracted to the warm room. When he left his friend's room was relatively warm and he in consequence suffered. A leak was discovered in a gas pipe in the road. In another case a man sleeping in a room adjacent to one in which two others suffered severely was himself affected. The rooms were separated only by a plaster and lath partition. He had no symptoms of note for 24 hours when he suddenly collapsed after unusual exertion.

Should the history be equivocal the pink colour of the patient or of some parts of the body if not all is highly characteristic. The finding of CO in the blood would clinch the diagnosis—the pink colour is readily apparent if the blood be diluted. It must be borne in mind that almost the whole of the CO may be removed by artificial respiration so that a negative finding does not exclude CO-poisoning if this has been performed.

CO in the air of the room may be tested for by shaking a large bottle through which the suspected air has been drawn with a little diluted blood. If it is possible to draw the air through the solution this is better. It can be done with a length of glass tubing and an ordinary aspirator. The glass tube should lead to the bottom of the bottle just below the surface of a diluted blood solution. The air is then drawn through with the syringe as if the bottle were being exhausted.

Treatment.—The indications are four, viz., oxygen, rest, warmth and stimulants. The patient must first of all be moved to a room in which the air is fresh. Oxygen may of course be introduced by means of artificial respiration and this must always be done in advanced cases but the oxygen percentage in ordinary air is comparatively low and pure oxygen should be used if it be possible. If the blood from the finger or ear shows a pink tint on dilution artificial respiration should be performed.

Rest is an absolute necessity and should be enjoined although the patient strongly disapproves and asserts that he is feeling quite well.

Warmth is of great importance and it is to be remembered that throwing open windows may introduce a very prejudicial factor if the patient be not at the same time well wrapped up. External warmth can be applied by means of hot blankets, hot bottles, etc., but the importance of internal application must also be borne in mind. Hot coffee enemata and draughts of the same fluid when the patient can swallow serve also as stimulants and are to be advocated.

Stimulants will naturally take the form chiefly of the heart stimulants, of these caffeine is the best and alcohol is not to be employed as it tends to hinder the oxygenation of the tissues.

Transfusion has been combined with bleeding with the idea of removing CO-hæmoglobin from the body but this is more quickly attained by artificial respiration and the practice was based on the old pathology which taught that CO could not be dissociated by oxygen. This is now known to be an erroneous idea.

Amyl nitrate has been used in some cases with advantage but it is a little difficult to see how it is beneficial unless it be by providing a larger supply of blood to the brain and with it a larger supply of oxygen. It might be useful as a temporary measure.

The probability of pneumonia supervening must ever be borne in mind and the prophylactic injection of a dose of pneumococcus vaccine would be in accordance with modern teaching although the writer is not aware that it has ever been advocated or used.

SULPH-HÆMOGLOBINÆMIA

Synonyms.—Enterogenous cyanosis, idiopathic cyanosis.

Definition.—A condition of the blood in which sulphur is combined with the hæmoglobin molecule.

Nature.—It is probable that this is a bacterial disorder but the organism has yet to be identified. It is true that Wallis has isolated an organism from the saliva of several cases which he could not find in the saliva of normal persons and that this organism forms nitrites from organic compounds of nitrogen. It is also true that the presence of nitrites in the blood might favour the action of intestinal sulphuretted hydrogen on the blood and so be responsible for the presence of sulph-hæmoglobinæmia. But there are several considerations which prevent one accepting this as the causal organism of the disease. It has not been isolated from the blood nor does it produce any effect when injected into animals. Moreover it absolutely refuses to grow in vitro at body temperature—requiring a lower temperature. It has not been isolated from the intestinal tract. Treatment with vaccines prepared from the patient's brand of this organism (a non-motile bacillus, gram negative) has been singularly inconclusive.

It is better therefore at present to say that the causal organism is not identified and to base treatment on a view of the pathology derived from clinical experience.

General Pathology.—The first essential for the onset of this disorder would appear to be a morbid condition of the intestinal tract and so simple a disorder as constipation would appear to be the commonest and quite sufficient. As a rule, cure of the constipation has meant disappearance of the cyanosis. On the other hand it must be admitted that there has sometimes been no marked constipation but even diarrhœa but even in these cases there has been evident disorder of the intestinal tract.

We will suppose—without being able to prove it—that this disorder is due to the development of some organism of such a nature that it allows the sulphuretted hydrogen of the bowel to act on the blood either by rendering the blood capable of reacting to the presence of sulphur or by forming some easily assimilable compound of sulphur.

Cyanosis will then slowly appear and will vary according to the growth of the organism or the intensity of its products. Thus we shall not be surprised to find frequent variations in the extent of the cyanosis and this is clinically the case.

Now in one case of this disease the cyanosis was noted to be present in the blood of the face and extremities but absent from other parts. This was proved to coincide with the absence or presence of the sulph-hæmoglobin spectrum in the blood of these parts. How is this to be explained. One is forced to suppose that the sulph-hæmoglobin was formed locally and since the localities were those exposed to the outer air (the cyanosis was worse out of doors) we must suppose that it was formed under the influence of cold. This might act by retarding the blood flow—as in other cases of cyanosis in which the extremities are most affected—or merely by reducing the temperature. It is noteworthy that the bacillus of Mackenzie Wallis only grows at room temperature, but this was never isolated from the blood. We are disposed to think that our hypothetical intestinal organism merely provides the material for the formation of sulph-hæmoglobin but that this does not act except where the oxyhæmoglobin is being vigorously reduced by the tissues, as it is in the ordinary course of affairs. This reduction would be more complete in the extremities when the blood flow was retarded and would explain the fact that in this case the cyanosis was only obvious in those parts. This is, however, rather of theoretical than practical interest.

Once established the cyanosis continues for many years with variations and even with complete disappearance at times. It has no lethal tendency of itself—only a very small part of the hæmoglobin is affected. The intestinal condition, however, is likely to get more serious as time advances and very offensive diarrhœa is one of the least uncommon signs of this. Later stercoral ulcers may occur and the disease then becomes a definite danger to life. It is therefore a matter of urgent importance to treat this intestinal condition and all the usual measures of procuring intestinal asepsis are reasonably employed.

Should these be successful the cyanosis will disappear and the pathology of the disease will be baulked of its conclusion by the intervention of the physician—whereby honour may be expected to accrue to him.

General Symptomatology.—The outstanding feature is the cyanosis and the exact tint of this has been variously described. It is certainly somewhat different in one case from the tint seen in another. There is one aspect of the colour which is invariable and characteristic. It is the association with intense pallor—this is also seen in methæmoglobinæmia but is not seen in the cyanosis of heart disease, etc. From the cases which have come under the author's notice the colour seems to vary from a lavender or mulberry hue to a greyish tint similar to that sometimes seen in silver poisoning. It is usually generalised but more marked in the extremities, *i.e.*, the ears, fingers and toes. The colour is especially well seen in the mouth where the epithelium is more transparent than that of the epidermis.

In one case seen by the author the cyanosis was localised to the face and the base of the finger nails but during cold weather became more extensive. This case is at present unique.

The cyanosis once established is usually permanent in the absence of treatment, but although it is always present to some degree it may vary in intensity from time to time. These variations do not appear to have any particular relation to the time of day, food, or other similar factors. They have, of course, been noted to occur during treatment but there is no evidence to attribute them to any particular drug or other therapeutic effort. Permanent disappearance of the condition has been brought about by methods which will presently be detailed.

The dyspnœa which is so prominent a feature of cardiac cyanosis is slight or absent in sulph-hæmoglobinæmia and this is due to the fact that the amount of hæmoglobin affected is always very small. There is a reducing substance present in the blood which prevents its ever reaching a greater concentration.

Dyspnœa may, however, appear on exertion—when it may be presumed that there is a greater demand for normal hæmoglobin owing to the comparatively rapid way in which the tissues are using up oxygen under these conditions.

The only other symptom of note—apart from those seen during an acute collapse—is constipation.

It is to be remembered that constipation is the usual symptom or manifestation of the abnormal condition of the intestinal tract, there is nothing, so far as we know, to prevent these conditions prevailing without giving rise to constipation at all. The practical bearing of this is obvious. Rigorous intestinal antisepsis should be ensured although the bowels may appear to act normally. This is the more urgent when we consider that the only cures of this condition which have been recorded were so obtained.

The constipation, if long continued, brings other evils in its track such as atonic dilatation of the colon and even ulceration. The breaking down of hard fæces by bacterial action and the concomitant irritation of the bowel wall may lead to a discharge from the anus of dark, offensive and blood-stained material.

The patient's general health is also generally affected adversely as would be expected.

In some cases sudden collapse has been a feature—the patient appears to be at death's door and restorative measures are hastily resorted to. But the patient does not die although the condition of apparent collapse may endure for some weeks. In such conditions oxygen given in a Clovers inhaler will be of value but generally speaking, oxygen is only of value in this disease for just this class of emergency.

Various hysterical manifestations are to be expected and weakness is always a prominent complaint. They will be met with the measures which seem most appropriate to the individual, but the weakness will last as long as the cyanosis does.

The blood seldom shows anæmia but has rather a tendency to polycythæmia—probably compensatory. Leucocytosis is variable and probably depends on associated conditions rather than on the disease itself. The spectrum of sulph-hæmoglobin (page 284) is found in the blood which is of a more or less purple tint.

Treatment.—The first and most important indication is to deal with the constipation. Unless this is done with success the disease will continue. If it is done with success the disease will cease. It seems strange that the whole secret of treatment should lie in so simple a procedure as the above but it is unfortunately the fact that it is so difficult to carry out with drugs alone that the disease has come to be regarded as almost necessarily incurable.

There is no need to detail the purgatives which may be tried as these include all those in common use and several others.

Perhaps a more useful point of view is that which looks at the question as a problem involving the restoration to a healthy condition of the large intestine—to remove scyballous masses which are found there will not necessarily have this effect. Considered from this point of view the problem is much the same as that presented by atony of the colon and by ulcerative colitis. Obviously the first measure from which we may expect much success must be in the nature of washing out the colon. When purgatives have been tried and failed and when dieting has proved of no avail lavage must be tried. If it seems politic to perform this by means of enemata this may be done but is not likely to be of much value as it is quite probable that the diseased area will not be reached—it is not so much restricted to the lower end of the colon as is often the case in ulcerative colitis but resembles more the lesions of atony of the colon—which are usually most severe at the cæcal end.

We pass then to the effectual treatment of the condition which is surgical. It is, however, quite right to try other treatments first although the liability to the formation of adhesions, etc., contra-indicates their too long continuance. The simplest surgical measure is undoubtedly appendicostomy which allows of direct medication of the bowel and has not the irrevocable nature of the larger operations to be presently mentioned.

When appendicostomy has been performed there are two indications, viz., to keep the fæces fluid or at least soft and to keep the bowel reasonably aseptic, *i.e.*, free from pathogenic organisms. The first, if it does not follow naturally from the performance of the second, may be effected by the injection through the appendicostomy opening of olive oil or some similar substance—castor oil may be used if the condition still proves obstinate. The second is best effected by the injection of large amounts of saline solution, for example a pint four times a day. The saline solution may be used as a vehicle for such drugs as Mag. Sulph. if peristalsis seems very deficient, but the latter is often productive of pain when given in this way and as a rule the saline suffices. Mild antiseptics such as boric acid may be employed. If Mag. Sulph. is used not more than 1/2 oz. to the pint is necessary although 1 oz. will not be likely to do any harm. Boric acid can be used in any strength up to saturation. If there seems to be any reason to suspect ulceration or this has been noted or suggested by scars seen at operation the use of 2 per cent. argyrol may be tried since it is often efficacious in ulcerative colitis.

If appendicostomy and the above indicated measures are not of avail the question of more radical operations must be considered and of these there are for practical purposes only two, viz., ileo-sigmoidostomy and excision of the colon. The latter is the more radical and the more certain but it is possible that it is unnecessary and it is certainly the more severe procedure of the two. No dogmatic statement can be made on the point and each case needs treating on its merits.

It will be noted that the above is merely the treatment of constipation in its most extended and logical form. All these measures have not been actually tried so far as reports on cases in the medical journals show but in at least two cases appendicostomy has proved of great benefit and has been followed by disappearance of the cyanosis. In any case it is difficult to see how any condition which arises in and is confined to the colon can very well persist after the colon is removed, so that the failure of other methods would fully justify resort to this.

It must, however, be mentioned that causes such as stricture of the rectum, etc., are to be looked for previous to any treatment of the nature outlined above as the cure of such may prove also the cure of the sulph-hæmoglobinæmia.

Although the above represents the most rational treatment at the present moment it is not likely to remain so forever—it has been suggested that there may be a micro-organism responsible for the sulph-hæmoglobinæmia if not for the whole disease.

Symptomatic treatment is mainly required during attacks of collapse and is such as is suitable to collapse in any condition and is in no way special to this disease. Any drug, such as quebrachu, which is alleged to increase the capacity of the blood for oxygen may well be given a trial.

If, as not infrequently happens, the use of some sedative drug seems desirable it is better to avoid the synthetic aniline drugs such as phenacetin, antipyrin, etc., as these may themselves produce cyanosis and bromide and chloral will probably suffice.

INFECTIVE METHÆMOGLOBINÆMIA

Synonyms.—Microbic cyanosis, enterogenous cyanosis.

Definition.—A condition in which owing to bacterial activity some of the oxyhæmoglobin in the circulating blood is converted into methæmoglobin.

Nature.—This is almost entirely conjectural and so of small importance to the clinician. It is to be regarded as an unusual complication of septic conditions, *i.e.*, a non-specific infective disorder. It may eventually prove to be specific but there is no such proof at present.

General Pathology.—This also is not on a very definite basis. There is no doubt that organisms cause the blood change and that their removal coincides with recovery. How they do it is another matter and the suggestion that the change is due to nitrites circulating in the blood is not altogether satisfactory although these are as a matter of fact found.

However this may be, there is no doubt that a certain amount of the oxyhæmoglobin is altered into its isomer methæmoglobin. Reducing bodies are always present in the blood or the tissues with which it comes into contact and these no doubt reduce the methæmoglobin—presumably taking its oxygen at the same time. The reduced hæmoglobin must then again become oxygenated before it can be reconverted into methæmoglobin. This means that there need be no great reduction in the oxygen-carrying power of the blood nor is this as a matter of fact the case, as shewn by the comparative absence of dyspnœa and of compensatory polycythæmia. The methæmoglobin gives the peculiar colour to the complexion. Where the alteration of the oxyhæmoglobin into methæmoglobin takes place we do not know. It certainly often depends on changes in the intestinal tract but this does not necessarily mean that it is changed in the portal system. It is probably formed in all parts of the body by the agency of some body in the general circulation. This could presumably act wherever oxyhæmoglobin was to be found and would therefore be most active in the arterial circulation.

There does not seem to be any increased destruction of corpuscles in the spleen so that we may surmise that they are not much damaged by the alteration of the pigment which they carry nor is there any particular reason why they should be. The pigment, methæmoglobin, does not leave the corpuscles as is the case in some hæmolytic anæmias nor are they found to be fragmented.

Recovery merely means the removal from the circulation of the body which causes the change to methæmoglobin and which is apparently of bacterial origin. With it the cyanosis vanishes and the condition of enterogenous cyanosis no longer exists.

Allied Diseases.—There is only one of importance, viz., sulph-hæmoglobinæmia. This seems to be almost precisely similar except that the abnormal change in the hæmoglobin is different, *i.e.*, into sulph-hæmoglobin instead of into methæmoglobin. It differs in the presence of constipation as against diarrhœa.

Etiology.—We know of no definite etiological factor except disorder of the alimentary tract. This usually precedes the onset of methæmoglobinæmia but in one case followed it, *i.e.*, colitis first became obvious in a severe form three months after the disappearance of the cyanosis. It had not previously been looked for or apparent. It became so severe that an operation was necessary for division of adhesions subsequently. This operation was also necessary in another case.

Age and Sex.—There are too few recorded cases to allow of any useful statement on this point.

General Symptoms.—Only those feature in which it differs from sulph-hæmoglobinæmia will be mentioned.

Firstly there is diarrhœa or colitis. In one case an organism of the coli group was isolated and Gaertner's bacillus has been isolated in a similar condition in rats. A bacillus of the coli group was also isolated from the blood in one case in which diarrhœa was a prominent feature. The colitis may be very obstinate and very severe.

Secondly there is sometimes a return to normal if a strictly milk diet be adhered to but this is not permanent and the cyanosis returns if a meat diet be taken.

There are no characteristic changes in the urine or fæces at present determined.

Blood.—Anæmia is sometimes met with in a marked form and a slight degree is to be expected due to the septic process. It must be borne in mind that in methæmoglobinæmia as in any other disease accompanied by diarrhœa there is apt to be some concentration of the blood due to loss of fluid and this may give an idea that the blood is normal or even supra-normal even when there is anæmia.

The anæmia is of the usual septic or chlorotic type, *i.e.*, there is a greater diminution in hæmoglobin than in red cells per cent.

Leucocytosis is usually present and depends on the septic process as does the anæmia. It varies in intensity as far as can be gathered from the few records. The spectrum of methæmoglobin (page 284) is found in the blood.

Course and Duration.—The disease is essentially chronic and may last for years. It is only terminated by the septic processs underlying it resolving, and intestinal sepsis seems to be of a peculiarly intractable nature.

Treatment.—This amounts to the treatment appropriate for the colitis or diarrhœa underlying the disorder—vaccines should be employed, if no particular organism can be recovered from the blood a vaccine should be prepared from the fæces. Appendicostomy with lavage of the colon will probably be necessary judging from the published cases. A strict milk diet may cause temporary disappearance of the cyanosis.

CHAPTER XVI

LEUCOCYTOSIS

POLYMORPH LEUCOCYTOSES

This is a blood symptom characterised by an increase in the relative proportions or absolute numbers of polymorphonuclear leucocytes.

It is present as a physiological phenomenon during digestion, after hot baths, after exercise and in a variety of other conditions not associated with disease. In none of these, however, do the total number of white cells per c.m.m. rise above 12–14,000 at the most so that there is not often confusion with pathological conditions. Physiological leucocytosis is usually of short duration.

Pathological leucocytosis (polymorph leucocytosis is frequently referred to simply as "leucocytosis" and will be so in this book) arises in many conditions of which the most important clinically are infective processes and malignant disease. The fact that it is absent in some and present in others of the acute fevers is of diagnostic importance—under the heading of various diseases the changes in each are dealt with. It also follows hæmorrhage.

Leucocytosis may occur very quickly—within a few hours—of the onset of toxic processes and is usually to be interpreted as a favourable reaction. Where it is absent in a disease with which it is known to be commonly associated the prognosis is very grave and the absence is interpreted as a failure of the body forces to mobilise against the invader. In chronic cases, *e.g.*, of abscess formation, in which the morbid process has ceased to extend, the leucocytic reaction may be very slight or even absent. The grave prognosis does not then attach as will be seen from the entirely different clinical picture which the patient presents.

Leucocytosis may reach as many as 236,000 cells per c.m.m. This is the highest count which the author has found mentioned in the literature and counts of above 100,000 white cells are very rare except in leukæmia. 15,000 to 50,000 is the common number in pyogenic infections. Relative leucocytosis is the term applied to the condition when there is no actual increase of polymorph cells above the normal but their relative numbers are increased. Thus a count which shows 90 per cent. of polymorphs in a total of 5,000 white cells per c.m.m. exhibits relative leucocytosis. The total number of polymorphs is obviously 4500 which is not above that commonly found. A count of 90 per cent. of 12,000 white cells per c.m.m. would be said to show both relative and absolute leucocytosis. Here the percentage of polymorphs is increased to 90 per cent. (relative leucocytosis) and the total number to 10,800 (absolute leucocytosis). On the other hand a count of 65 per cent. polymorphs in a total of 20,000 white cells shows no relative leucocytosis but an absolute increase in the polymorphs to 13,000 per c.m.m. It will be noticed that in order to achieve an absolute increase in polymorphs and yet have a normal proportion of these cells compared to the proportion of the other cells there must be also an absolute increase of some other variety. This is called a mixed leucocytosis.

The occurrence of leucocytosis is further dealt with under Diagnosis in Surgical Diseases (page 334) and under Various Diseases (page 356).

EOSINOPHIL LEUCOCYTOSIS OR EOSINOPHILIA

This may be relative or absolute and consists in the presence of abnormal proportions or total numbers of eosinophil cells. The usual number of eosinophils is 1–2 per cent., and 150–250 per c.m.m. In children the number is increased and also during menstruation.

Pathologically eosinophilia occurs in many conditions. It should lead one in the first place to expect asthma, skin disease or parasitic disease especially alimentary parasites. If these can be excluded and still the condition of the patient affords no satisfactory reason for an eosinophilia it should be remembered that eosinophilia also occurs in chorea, in Hodgkin's disease and in some of the acute infective conditions. If it occurs in association with glandular enlargement Hodgkin's disease is a very probable diagnosis.

The highest eosinophil count known to the author is 40,000 per c.m.m. and this followed an injection of tuberculin. A percentage of 90 has been recorded. The more usual figures are under 1500 and 20 per cent. A fair number of cases of parasitic infections exceed this limit.

LYMPHOCYTOSIS

In a few conditions lymphocytosis is comparatively common, *e.g.*, in pertussis at any age and in various children's disorders. It is also met with after pilocarpine has been given and is present although not usually in an exaggerated form in goitre, especially exophthalmic goitre.

In all these conditions there is an increase in the number of circulating lymphocytes with (mixed leucocytosis) or without an increase of some other variety of cell. The lymphocytes are normal lymphocytes and degenerate cells are not met with as is the case in leukæmia.

There are however certain cases, which are rare, in which a lymphocytosis makes its appearance during some infective disorder, *e.g.*, streptococcal infection. The lymphocytes may then reach a very high percentage although it does not follow that the total number is increased very markedly. Such cases may show a lymphocyte percentage of 80–90; this is a great deal higher than is met with in any other condition except lymphæmia. In the latter disease there is very often a percentage of lymphocytes exceeding 90 per cent. In a single case of this sort (infective lymphocytosis) Cabot has reported that there were many cells which showed signs of division and even one typical mitosis amongst the cells in the blood stream. From the blood alone it would be impossible to distinguish such a case from one of lymphæmia although Cabot remarks that there was a notable absence of degenerate cells. These, however, are not an absolutely safe criterion.

The practical point is that where there is an obvious infective focus, especially if there is lymphangitis, the presence of a lymphocytosis may be expected in a few cases and an unusual blood picture must not necessarily be taken as that of leukæmia.

MIXED LEUCOCYTOSIS

This blood symptom is characterised by a simultaneous increase in either polymorphs or eosinophils and lymphocytes. A mixed eosinophil leucocytosis is very rare but may be present when two diseases co-exist such as helminth infection and hæmorrhage.

A mixed polymorph and lymphocyte leucocytosis is met with during digestion in some cases and sometimes in whooping cough.

It is obvious that the leukæmias may present a mixed leucocytosis but the fact that one was dealing with a case of leukæmia would remove it from this class of leucocytosis.

LEUCOPENIA

This is another blood symptom and is characterised by a diminution of the circulating leucocytes. In a few cases prolonged search of several films has failed to reveal more than two or three leucocytes. These are extreme cases but a count below 2000 per c.m.m. is relatively common. As the diminution is usually at the expense of the polymorphs it is very common to find a relative lymphocytosis in leucopenia.

Leucopenia occurs in some of the acute infections, in many chronic anæmias and in acute aplastic anæmia. It is perhaps particularly characteristic of splenic anæmia of adults.

CHAPTER XVII

CHLOROSIS

Synonym.—The green sickness.

Definition.—A morbid process appearing at or about the time of puberty, characterised by certain nervous manifestations, by an increase in the total volume of the blood and by a relative diminution of hæmoglobin.

Nature.—Chlorosis is an exaggeration of the processes occurring naturally at puberty, processes of which we unfortunately have very little accurate knowledge. We do know, however, that there is an increase in blood volume, a relative diminution in hæmoglobin and a change in nervous activity. All these are much more obvious and more profound in the female and this accounts for the fact that chlorosis is very rarely evident in the male. The changes incidental to puberty, of which the onset of menstruation is only one and not necessarily either the first or last to appear, probably depend on an alteration both in quality and quantity of metabolism, and this in turn depends on the newly developed internal secretion of the genital glands. The factors allowing of an exaggeration of normal processes are in part peculiar rather to the family than to the individual. They consist of a lessened nervous stability, a blood-forming bone marrow which is unable to respond adequately to the exceptional calls made upon it and a variation in the internal secretion above mentioned. This variation is probably in the direction of excess of an otherwise normal secretion. Constipation acts more by hindering the excretion of superfluous fluid and metabolic products than in any direct causative capacity. Menstrual hæmorrhage is in some an added drain on the marrow but certainly one of very little moment.

Age.—Chlorosis usually makes its first appearance between the ages of 14 and 25, after the latter age a first attack of anæmia should not be diagnosed as chlorosis without very good reasons. More important than the exact age in years is the relation of its onset to that of puberty. When a normal maturity of the body has been reached without an attack of chlorosis the individual is immune.

Sex.—There has been much controversy about the occurrence of chlorosis in the male. It does occur but is very rarely sufficient in degree to call for the attention of the physician.

Predisposition.—Beyond the predisposing factors already mentioned we know of none except the common causes of ill health but there is a distinct tendency for the disease to affect more than one member of large families. There is no evidence to incriminate those frequent scape-goats, gout, syphilis, tuberculosis, etc.

Onset.—This is most often gradual, as are the changes of puberty. In about one in ten the onset is more sudden and is consequently ascribed to some particular adverse factor in operation at the time. Such factors are too numerous to mention and their significance, if any, is very obscure.

General Symptomatology.—The most striking symptom is the pallor. This must be seen to be appreciated and is neither the dead white of acute hæmorrhage nor the yellowness of chronic anæmias. It is much more like that of œdematous tissues with a slight admixture of a yellowish tint. A deceptive red flush is not infrequent. Only a very fertile imagination can, as a rule, detect any green colour. The subcutaneous fat is not lost as a rule, certainly not in early cases; it may even be increased in amount.

Indigestion, weakness, palpitation and dyspnœa are among the symptoms which first bring the patient to seek medical advice. Elevation of temperature is often seen but is variable in degree, extent, persistence and frequency of occurrence. Generally speaking, when present it resembles that seen in most other anæmias and conforms to no particular standard.

The disposition often changes and may be the subject of comment on the part of the parents or friends.

The symptoms will now be more fully dealt with under exact headings.

Circulatory System.—Organic heart lesions are exceptional and can only be viewed as accidental complications of the disease but on the other hand what is aptly called nervous irritability of the heart is often met with. This shows itself as palpitation of very variable incidence; thus one patient will always have palpitation, another only when excited and a third after the slightest exertion. In some the pulse rate is actually increased, in others there does not seem to be any organic basis for the palpitation discoverable. In the same way there may be permanent increase in the frequency of the pulse or paroxysmal attacks of tachycardia, both without any subjective symptoms. The heart often appears enlarged but is not so in reality. The increased superficial dullness results partly from deficient expansion of the lungs and partly from displacement of the heart. Examinations by the X-rays reveals the latter. Blowing systolic murmurs are to be expected in all but the mildest cases. They are subject to all kinds of variations and have no very marked preference for one or other of the valves. They are here one day and gone the next, are sometimes intense and at others hardly to be distinguished: they usually vanish with the other symptoms but may rarely outlast them for a short time.

There is nothing characteristic about the pulse except its variability although it is usually rather full and some say that there is a tendency to dicrotism.

The arteries are not abnormal in the great majority of cases but a general underdevelopment has been described. If this is present and detected it must be regarded as a complication. A venous hum—the bruit de diable—is to be heard at some time in at least half of the cases and a similar bruit or even a double sound may be heard in the femoral artery.

The vaso-motor mechanism of the smaller vessels seems to be very often unstable and gives rise to a somewhat characteristic train of symptoms. These are trivial in degree in most cases but occasionally a patient is met with in whom they constitute the chief burden of her disease. Sensations of cold and heat without adequate physical basis, sudden blanching of the fingers, painful hyperæmia of the extremities and an excessive liability to chilblains may be most prominent in different cases. It is not always the case that these disappear when the chlorosis is cured and it may be that they are only exaggerated and not originated by its occurrence.

Œdema is not common but it is of importance to remember that it does occur because the clinical picture of nephritis may be closely simulated. It usually affects the feet and ankles but may appear in the hands, face or eye-lids.

A tendency to thrombosis is well known to characterise chlorosis. At the same time it will prove rare in individual experience. As we have no reason to suspect an abnormal tendency to clotting on the part of the blood it is reasonable to suppose that many of these thrombi are infective. This has been proved in some cases but hardly explains why even infective thrombi should be more common in chlorosis. Certainly, however, it is a complication to be looked for and as it not infrequently affects the cerebral sinuses may cause the death of the patient. In other situations the thrombi seldom do any grave damage.

Respiratory System.—An excitability of respiration is often noticed similar to that of the pulse and heart and similarly devoid of any sufficient organic basis as far as can be determined. Acceleration of the breathing may occur without any preceding exertion but on the whole this is uncommon and the excitability partakes more of the nature of excessive response to trivial stimuli. A sense of dyspnœa and oppression is often a source of distress to the patient. In the majority of cases the respirations are moderately accelerated throughout their illness and this may represent an attempt to compensate for the relative impoverishment of the blood. The variations in respiration above mentioned stand apart from this.

Shallow breathing with deficient expansion of the lungs is often to be detected.

Alimentary System.—The physician's attention will often be directed to this system for with the exception of the hæmopoietic no other is so frequently affected in chlorosis. Fortunately chlorosis itself seldom causes any serious lesions although the coincident occurrence of gastric ulcer is often noted. This will be considered as a complication later on. The gastric symptoms may be very prominent although they do not often lead to serious damage. Nausea and vomiting occur in nearly 50 per cent. and are often accompanied with considerable pain. The latter may be nearly always present or only noticed after meals. There may be tenderness in the epigastric region or actual pain there, in other cases the only pain complained of may be colic of irregular incidence and intensity.

It is well established that hyperacidity of the gastric juice is found in many cases.

Gastroptosis, gastric atony and dilatation are all of rare occurrence.

Perversion of the appetite is more common than any actual deficiency. The perversion extends not only to the desire to eat but also to the constitution of the meal. A desire for sour articles of diet is especially frequent and may sometimes be effectually combated by the administration of chalk—in the form of a pill. There is no limit to the peculiar cravings of these patients, thus some devour bird-seed with avidity while others prefer vinegar, slate pencils or sand.

It is customary to insist on the tendency to constipation in chlorotics but there can be little doubt that this is over estimated and insisted on without taking into consideration the habits of the rest of the population in this matter. Diarrhœa may be present but is rare, probably in nearly 50 per cent. there is no abnormality in the action of the bowels.

Urogenital System.—As one might expect the abnormality of internal secretion is not very seldom accompanied by abnormality of the external genitals. The frequency of such developmental errors is, however, almost impossible to estimate owing to the difficulties in the way of a sufficiently large number of examinations. Disorders of menstruation are almost the rule and the commonest of all is suppression or diminution of the flow. Pain is less often complained of but it is nevertheless fairly frequent. Excessive loss is unusual. Leucorrhœa is very often present.

At the time that the patients are first seen it is not always the case that menstruation has appeared and it is in quite a small number that the onset of chlorosis is exactly coincident with that of menstruation. This is not a matter to wonder at as might seem to be the case at first sight, for chlorosis bears a constant relation to the inception of altered growth at puberty but menstruation a very variable one. The latter is merely a convenient objective phenomenon to date from: this is sometimes not sufficiently realised when theories of chlorosis are under discussion.

Polyuria is not rare and may occur more particularly after each menstrual period. During menstruation on the other hand there may be a relative suppression, but neither at this nor at any other time in the course of the disease is the latter a serious symptom—unless true nephritis is present as a complication. The general tendency is all the other way and this is not surprising when we remember the excess of fluid in the body and blood stream. Even when the intake of fluid is lessened the falling off in the amount of urine is not nearly so large as the diminution of intake would lead us to suppose. Polyuria is not marked as a rule until improvement begins to occur.

Urine.—This is usually pale and poor in pigment and the pigments are never increased. Excess of nitrogenous excretion may be noted and albuminuria is very often found but is not marked. Cyclic or adolescent albuminuria is not especially frequent. Casts, mostly of the hyaline variety, are found in many cases but have no evil significance. A slight cloud of albumen and one or two hyaline casts are the usual findings.

Nervous System.—Although troubles in connection with the alimentary system are most frequently complained of, it is the nervous system which is most often disordered—may, in fact, be responsible for the gastric symptoms as well as for those referred on first sight to other systems. Nervous disease with a recognisable organic basis is, of course, rare and to be regarded as something independent in origin of the chlorosis. Diminished and perverted activities of the mental faculties in general are apt to be a source of considerable difficulty to the medical attendant. A mildly neurasthenic disposition and excessive irritability are the severest forms met with at all commonly but the occasional occurrence of acute dementia and other profound disorders of the mind is worthy of mention as shewing the reality of these symptoms. The mental affection is not parallel to the degree of anæmia but seems to depend more on the previous mental stability of the patient, just as the degree of anæmia depends to some extent at least on the previous strength of the hæmopoietic organs.

Although "hysteria" is rarely absent in some form or another it is not to be expected that it will always show itself in actual abnormalities of function or only in certain parts of the body. On the other hand it usually exists rather as a general disposition to make the worst of any disorder present and only more rarely extends to the creation of new ones. Strangely enough the exaggeration of mental anguish is not in proportion to the exaggeration of bodily ill so that the chlorotic patient is not—unless neurasthenia be pronounced—apt to insist on his symptoms and it may sometimes require direct questions to elicit them. For this the profession should be grateful for the number of the symptoms of chlorosis is legion.

Pain is not very often present apart from that referred to the alimentary system but may be more or less prominent. It is felt in the back by some, in the chest or between the shoulders by others while a third class experience the well-known "pains all over." Headache is frequent and may be hard to treat when it is continuous but it usually vanishes as the blood condition improves.

Insomnia, if complained of, should be given every attention for neglect to do so is a more serious setback to the patient than is the neglect of almost any other symptom. It occurs in about 1 per cent. of cases in a form requiring treatment.

Other symptoms in reality dependent on nervous derangement are treated of elsewhere, *e.g.*, angiospasm, etc.

Ears.—Tinnitus, dizziness and similar subjective symptoms are not rare but may be of such slight degree that no complaint is made of them. In rarer cases they are a source of great annoyance but permanent harm never results. They have no ascertainable organic basis.

Eyes.—Here the symptoms are not purely subjective and may place the patient in some danger. Those that are subjective are chiefly sensations of blackness and of spots or flickerings before the eyes. They are momentary but may be often repeated. Fainting fits may follow or precede them. Very rarely total blindness may be present for a time, it is not due to organic lesion but is a manifestation of "hysteria."

Among the more serious symptoms the least is a weakness which occurs after reading, etc., more readily than in normal individuals. With this some degree of conjunctivitis may coexist. Scleritis is said to be not uncommon and such serious disturbances as irido-cyclitis, choroiditis and the formation of vitreous opacities may follow even if they do not more closely depend on the occurrence of chlorosis.

A variety of changes are described as taking place in the fundus in different cases, *e.g.*, a condition resembling albuminuric retinitis, optic neuritis and even optic atrophy. Usually the background of the eye does not show any greater abnormality than pallor with increased transparency of the vessels. Hyperæmia is rare and hæmorrhages present only in the most severe cases. The eye symptoms may lead to a suspicion of cerebral tumour. Cerebral thrombosis may be similarly suggested and it is not to be forgotten that this may be present as a symptom of the chlorosis and may prove fatal.

Paralysis of the external ocular muscles has been occasionally recorded and when present should raise a very strong suspicion of thrombosis.

Vision is not often interfered with but a mild degree of hypermetropia is more frequent than one would expect.

Skin.—Acne simplex is only too common nor is it more amenable to treatment in chlorosis than it is in other conditions. Seborrhœa is the next most common abnormality, excluding those dependent on vaso-motor irregularities, other affections of the skin are uncommon. Of these general hyperhydrosis is the most distressing to the patient; fortunately one can hold out the hope that it will disappear with the cure of the chlorosis. If it should not do so the services of a reliable medical radiographer should be requisitioned. There appears to be some tendency to urticaria and the variety known as "factitia" may be met with, too. Pigmentation is not common but is sometimes noted about the flexures or in the substances of warts which vanish when the blood condition improves. Chronic eczema can hardly originate as a result of the chlorosis but it is certainly unfavourably affected and treatment of the general condition is of more importance for its cure than local applications. Among other skin disorders are trophic changes such as brittleness of the nails, purpura and others of even less frequent occurrence.

Lymph Glands.—These show no abnormality.

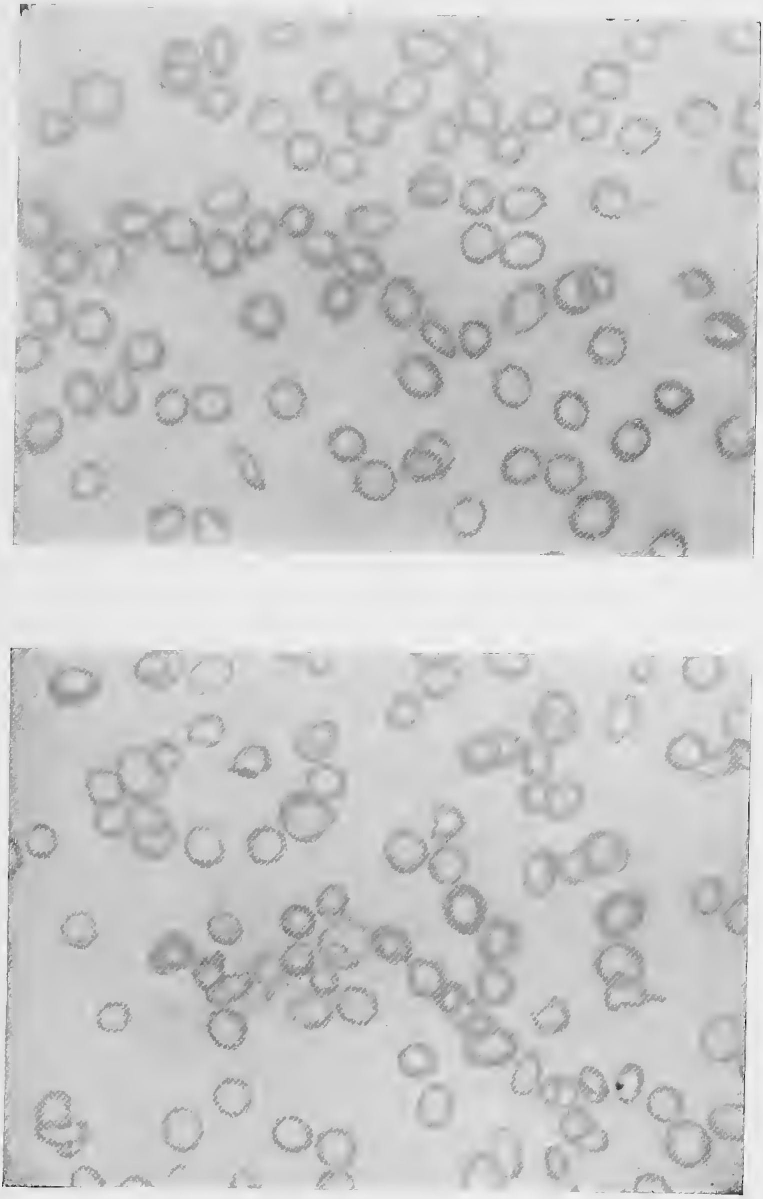
Spleen.—In about 10 per cent. of cases there is a very moderate enlargement present but this is not comparable to the enlargement found in many blood diseases. It is due to a hyperæmia and speedily vanishes when the patient's condition improves under treatment. A very large spleen should be considered symptomatic of some superadded disorder.

Ductless Glands.—The only one showing any abnormality at all commonly is the thyroid and this will be dealt with under the heading "Complications."

Blood Condition.—The salient point about this is the fact that the plasma is greatly increased in amount so that by diluting the blood it produces the illusion of anæmia. As a matter of fact there is in the early stages an actual increase of corpuscles in the body, the hæmoglobin is not increased to the same extent but may also be in excess. Until recently this was not demonstrable by any methods at our disposal although it had been suggested by several students of the disease. These changes are merely an exaggeration of those normally taking place at puberty.

Later the bone marrow no doubt feels the strain of working under difficulties and the onset of a certain degree of true impoverishment of the blood occurs. That this takes place the earlier owing to some congenital weakness of the marrow there is at least good reason to believe. Nevertheless the strain of the increased stimulus in chlorosis might weaken even a hæmopoietic system of the most unimpeachable character.

That part of the marrow which is concerned in the production of white cells seems to be unaffected in the early stages but may later on share any deterioration which the red marrow is undergoing; then a leucopenia results with relative increase



Figs. 38 and 39.—Blood in chlorosis.

of those cells which are not formed in the marrow, viz., the lymphocytes.

It is to be remembered that strictly speaking hypertrophy rather than atrophy is characteristic of the bone marrow of chlorosis and when atrophy does set in it is due to the long-continued strain of an excessive stimulus and to various other causes which are not part and parcel of the chlorosis, *e.g.*, prolonged inactivity, malnutrition and gastro-intestinal disorders.

The red cells, when the patient comes under observation, are commonly about 4,000,000 per c.m.m. but may be above the normal figure or more rarely very considerably below it. They are slightly smaller than normal and stain feebly owing to their small hæmoglobin content. Various abnormalities of staining may also be observed and a few cells much larger than the normal are not difficult to discover. Variations in shape are very frequent but quite slight in degree. Nucleated red corpuscles are not at all uncommon and a prolonged search will nearly always bring a few to sight. In some cases they exist in large numbers but this is not the rule. Megaloblasts are rare but not unknown and not of any dread significance.

The hæmoglobin is often less than half as much as we should expect from a consideration of the number of red corpuscles and may be even 20 per cent.–30 per cent. when the red corpuscles are practically normal. This is very characteristic of the disease as a similar disproportion is seldom seen in any other condition.

The white corpuscles may, as above mentioned, be reduced in number in severe cases but are usually about normal. In the former case a relative lymphocytosis is to be looked for. The presence of an increase of white corpuscles may occur from comparatively small causes but is then transitory; if such an increase is sustained some complication is imminent or has already occurred.

It may here be again emphasized that the blood deterioration is apparent and not real in the early stages and that it is a symptom of chlorosis just as gastric disturbance is and not the fons et origo mali to which all other symptoms are to be traced. True, it produces symptoms of its own but these should be kept in their proper position and not given the first share of attention.

Course of the Disease.—Chlorosis does not reach its acme at one attempt but as a rule progresses irregularly. There are usually three or four halts and fresh starts before it is fully established. These are not necessarily so marked as to be obvious clinically and in consequence the picture of a progressive anæmia is most familiar to the majority of physicians. The restoration to health is similarly slow but more regular. This restoration may be absolute or it may never be quite complete before a return of the old symptoms is manifest. It is the fortunate ones who escape with only the one attack, most people have recurrences and these may even continue to the time of the menopause. In an average case the initial attack is recovered from well within six months, in a large number within four. Two, three or four weeks may suffice to produce a normal count of red corpuscles but the hæmoglobin lags behind and even in mild cases may not reach 100 per cent. for six or more weeks.

In the case of strong girls recurrences may occur at longer and longer intervals but in the weakly the intervals may shorten until a chronic state of anæmia results. This is sometimes very difficult to overcome and the possibility of complicating factors is always to be borne in mind. Moreover the recognized complications are more likely to occur in these cases and the predisposition to intercurrent disease is more marked.

Termination.—The majority of cases terminate in recovery. In a few a chronic state is reached but even this will eventuate in recovery if complications do not occur.

Death as a result of chlorosis is very rare and is almost always due to cerebral thrombosis. Sometimes intercurrent diseases carry off the patient but for this termination the chlorosis can only be held responsible in as much as it exerts some predisposition.

Complications.—As has been frequently mentioned chlorosis predisposes to other diseases and particularly to the acute infective disorders: from these also chlorotics stand in more danger than do those not so affected. The course of infections is more severe and the termination less often favourable. Complications such as endocarditis, otitis media and paralysis seem more likely to occur.

Chorea has a special preference for chlorotics or at least for anæmic persons.

Gastric ulcer is generally held to be more frequent among chlorotics but as a matter of fact chlorotics do not suffer more than the rest of the community: but although gastric ulcer is not particularly frequent among chlorotics the latter may present most of the classical symptoms while the former may suffer from severe anæmia; there is consequently plenty of room for confusion.

Basedow's disease—in a mild form as a rule—is quite frequent. The symptoms usually met with are enlargement of the thyroid, increased pulse rate, hyperhidrosis and tremor. Exophthalmos is more rare. It is likely that these symptoms depend on the influence of the ovarian secretion on the thyroid leading to a heightened activity, and viewed in this light should cause little surprise when they developed during the course of chlorosis. In some cases the symptoms of hyperthyroidism persist after the chlorosis is cured.

Various disorders occur which may be regarded as complications or as dependent on the nervous disturbance which forms a part of the disease. Such are tic douloureux and various forms of mental disorder approaching insanity. These sometimes seem subject to variations which depend on the degree of anæmia present but have otherwise no very definite relation to the chlorosis as such.

Diagnosis.—This rests on the discovery of the relatively great diminution of hæmoglobin, the onset of the anæmia in a woman at the time of puberty, its rapid development without obvious cause and finally on the curative effect of iron administration. The co-existence of peculiar nervous symptoms and a history of similar anæmias in other members of the family are hardly less important.

The diagnosis is not difficult when chlorosis is suspected but in some cases the resemblance to other disorders is so great that the greatest care is necessary if a mistake is to be avoided.

Certain states which may lead to confusion will now be mentioned with a brief indication of the steps on which a differential diagnosis must be based.

From *tuberculosis* by the results of physical examination and, if this is negative, by the aid of an injection of tuberculin.

From *anaemia due to intestinal parasites* by a search for the latter.

From *anæmia due to hæmorrhage* by careful questioning and if necessary by examinations of the fæces for "occult" blood.

From *symptomatic anæmias* other than those mentioned by elimination of all factors which might cause anæmia and by a consideration of whether they exist in a degree comparable to that of the anæmia.

From *early cerebral disease* by the presence of localising signs: the diagnosis in the absence of these may be very difficult.

From *unsuspected pregnancy* by suitable examinations after first suspecting it.

From *neurasthenia* by the examination of the blood.

From *nephritis* by the examination of the urine.

From *hyperthyroidism* by the more marked character and persistence of the characteristic symptoms.

It should never be forgotten that anæmia is rarely due to one cause alone and that consequently even in chlorosis it is worth looking for others.

Treatment.—For once the first place in the treatment of disease can fairly be given to drugs. In chlorosis the administration of iron is indicated in the most unmistakable manner and to withhold it is malpraxis. Having said so much it is necsary to insist that the man who trusts to iron alone is not acting fairly to his patient. The regulation of diet, exercise, and rest is also of very great importance. With regard to the administration of iron there are a few rules on which the experience of years has put the stamp of approval. These are chiefly three:

a. That it should be in small doses at first and discontinued as slowly as it was begun.

b. That it should be given regularly.

c. That large doses are better than small.

A suitable amount of iron to be taken at the end of three weeks is ten to twenty grains of the exsiccated sulphate; it does not seem to make much difference which of the amounts is chosen but less than ten may prove insufficient. If iron does not do all that is expected of it arsenic may be given as well and in the form of arsenious acid may be conveniently combined with the iron pill. Beyond this the drug treatment of chlorosis is not in any way specific but a few of the more useful drugs in the symptomatic treatment may be mentioned.

For constipation the regulation of the diet is often the best treatment, as it is in cases of gastro-intestinal disturbance such as are commonly ascribed to the iron taken. If iron is given in accordance with the rules laid down bad results are a rarity, but in those who have been accustomed to buy Blaud's pills themselves and in quantities dictated by their financial circumstances and passing fancies they are not unnaturally common enough. If attention to the diet is not enough to keep the bowels open regularly there are many drugs to choose from. Magnesium sulphate has a particularly good reputation and when it is remembered that we are dealing with a disease characterized by the presence of too much fluid in the body this reputation is the more readily understood. If magnesium sulphate proves too drastic, and this may well be the case, there are others at hand. Of these Cascara sagrada and Extract: glycyrrhizæ are to be recommended. Care must be taken to avoid any excessive stimulation of the intestinal tract for it is always prone to get out of order in chlorosis. It is a cruel mistake to let the giving of purgatives be the main treatment of the disease.

For gastric disturbance the administration of dilute hydrochloric acid has sometimes been found of value, it is to be given about half an hour before meals. Why it is successful in some cases in spite of the frequency of hyperacidity in chlorosis is not well explained. The fact remains. For hyperæsthesia of the stomach and intestine belladonna has many supporters and it may be combined with strychnine to keep the muscular tone up to the mark.

For anorexia a bitter tonic may be given and the use of chalk in cases of perverted appetite has already been mentioned.

Small doses of bromide may be needed for the nervous symptoms if these become unduly prominent, but the routine use of anti-neuralgic drugs for headaches, etc., is to be condemned, as these are precisely the sort of patients who are likely to make a habit of using them. Rest in bed is excellent for headache and the analgesic drugs can be reserved for acute pains such as those of facial neuralgia.

For fainting attacks the use of small capsules of acetic ether (grs. iii or gr. iv) is good but the position of the patient and the avoidance of conditions likely to lead to attacks is better.

The treatment of other symptoms in chlorosis is in no way different from that which they demand in other diseases but the general management of the case has yet to be mentioned. In families which have an obvious predisposition to chlorosis it is well to indulge in prophylactic treatment and such matters as choice of residence demand more care than is the case in families not so predisposed. On the whole, high altitudes appear to be better than low, and damp or goitrous districts are to be avoided. Country life is not so much better than that of the towns as would be expected but adverse hygienic conditions are more likely to occur in the latter and this affords a reason for avoiding it if possible. The seaside is better than the country.

Mental and bodily fatigue are to be carefully avoided but this should not be made an excuse for avoiding the necessary modicum of occupation and exercise.

Equally, since excessive demands are made on the organism at puberty, the diet requires supervision not only in those in whom the disease has already declared itself but also in those who are suspected of some predisposition to it. It is well to begin the day with a meat meal for this will do much to combat feelings of faintness later. It will seldom meet with the approval of the patient at first but must be insisted on, and the physician can look for his policy to justify itself in the eyes of his patient later on. The rule about the other meals which is of most importance is that they should never be too large and in consequence must be more frequent than normal in many cases. Three or four hours is quite as long an interval as should be allowed. All meals must be followed by a rest in the recumbent position either on a couch or in bed. The intake of fluids at meal times is usually too much and is to be restricted.

There can be no doubt that the psychic value of an ordered regime is one of the indications for this careful study of the diet question. The above rules apply for the average case but exceptional cases are sometimes met with and these need particular modifications.

Thus in cases of emaciation it is quite useless to load the stomach with food for which the patient has no appetite and first attention should be given to the question of improving the latter. Change of surroundings and a tempting diet will often effect this when other measures have failed. As regards the sort of food which is indicated we can lay down the rule that foods with a large nutritive value compared to their bulk are indicated. Such foods are butter and cream while carbohydrates by no means fulfill these indications. Alcohol in small doses is indicated in these if in any cases.

On the other hand we may meet with cases of excessive obesity when it is to be remembered that this is in part normal. For the rest, fats and alcohol are to be avoided and fluids restricted. Elimination of fluid should also receive attention.

For gastric disturbance the drug treatment has been already indicated but it is necessary to state that it does not afford a contra-indication to the use of iron. If, after five or six weeks of an iron course, the gastric symptoms persist the question of ceasing to give iron or of giving it by some outer route may be properly considered, but to omit it in every case of gastric disorder is to jeopardise the treatment of 50 per cent. from the very start. The meals should be made smaller than before and the intervals less, and fats and butter are to be given as generously as possible. For constipation the addition of fruits and vegetables to the diet is required and this is also of value as supplying iron in the form in which the body is most accustomed to it.

Rest in bed is in this, as in so many diseases, an all-important part of the treatment and should be insisted on in all cases when this is possible. In the stage of recovery moderate exercise is good but in the earlier stages it is above all necessary to husband the strength of the body.

Patients will sometimes enquire whether they should take cold or other baths. The physicians advice should include a warning that all forms of shock to the system should be avoided. Very cold baths are therefore not to be recommended but warmer ones of short duration will have a desirable stimulating effect. Carbonated baths such as are obtainable at a number of spas have a similar effect, in fact spa treatment is beneficial in many ways.

There are some less frequent methods of treatment which have been tried and for which good results are claimed with a good show of reason.

Systematic hot-air baths are recommended because of the sweating which they cause and the theoretical basis of this treatment is as sound as that of giving saline cathartics, and it is also free from many of the drawbacks of the latter. A rest for at least an hour should always follow a hot-air bath; a tendency to fainting is a contra-indication.

The application of hot packs and diaphoretic agents has a similar basis and about the same measure of success.

Venesection has been practised and is capable of giving much benefit both by its well-known stimulating effect on the marrow and by the loss of fluid which it occasions. At the same time it will be obvious that a method apparently so paradoxical is not applicable to every patient.

Lumbar puncture has been recommended with the same object, viz., that of withdrawing fluid. We would strongly dissuade anyone from trying it as it has sometimes the most unexpected effects on the patients. Persistent vomiting and headache after it are by no means unknown.

Finally it may be admitted that much of the treatment outlined above is more ideal than practical and is not applicable to the circumstances of the poorer patients. Even with these, however, rest should be as much emphasised as is possible and the course of iron can be made regular and consequently beneficial.

CHAPTER XVIII

HÆMOPHILIA

Definition.—A disease, usually congenital and hereditary, manifested by effusions of serum and corpuscles into the tissues, especially the joints, and by deficient coagulation of the blood exemplified by uncontrollable hæmorrhages with apparently insufficient causes.

Nature.—This still requires elucidation. It seems, on the whole, to be a defect in some substance necessary to the proper coagulation of the blood. It must, however, be borne in mind that chlorosis, to which it presents certain very interesting analogies, also appears to be due to a defect but is in all likelihood due to quite a different abnormality which may be conjectured to be of the nature of an excess of some secretion normally supplied to the blood of the female during the fertile period of life.

Both hæmophilia and chlorosis are diseases of fertile families, both are transmitted by the female, in the former by the unaffected female to the sons, in the latter by the affected female to the daughters. Both show a tendency to spontaneous amelioration in adult life and in both apparently unaffected members of the families are found on examination to show signs of some lesser degree of the disorder. Neither seem to be primarily concerned with the corpuscles but with the plasma. Finally both appear to be quite independent of any change whatever in the environment of the patient, using this term in the broadest possible sense, to be in fact independent of the continual adjustment of internal to external conditions which constitutes the bases of the great majority of known diseases. No one can at present say how valid these analogies may be, they are certainly striking and of interest.

General Pathology.—This is, unfortunately, very difficult up to a certain point and very simple afterwards. This point is the occurrence of hæmorrhages. Why they occur we do not know—deficient coagulability of the blood, which is proved to be present, can hardly explain why a hæmorrhage occurs although it may afford sufficient reason for its continuance. The supposition that there must have been a trauma antecedent to all hæmorrhages is hardly borne out by facts. It is true that there is hardly a position in the body from which hæmorrhage occurs which may not be supposed to have been the site of some minimal trauma. But if such a trauma is held to be the all-sufficient cause of the hæmorrhages we have yet to explain why the whole body is not suddenly suffused with blood—why, for instance, the mere act of sitting down does not render a repetition of the act impossible without sitting on a large hæmatoma. Moreover there is an especial tendency for hæmorrhages to occur at night when all traumata are less likely to be encountered.

Leaving then the question of the cause of the hæmorrhages to be settled when it may, we can face the pathology of the disease from the onset of hæmorrhage. It should be first mentioned that the term "hæmorrhage" includes effusion of serum and diapedesis of corpuscles without apparent lesion of vessel walls and in such proportions that rupture of a vessel seems out of the question.

The onset may follow a trauma or be spontaneous. In either case it shows little tendency to cease and the blood is observed to clot indeed, but to clot less quickly than is the case in normal persons. Consequently the mouths of vessels are not closed and hæmorrhage continues. Especial danger is to be apprehended when the bleeding point or surface is in such a position that there is no natural compression of the wound by the elasticity of the tissues, such as the skin, or increase of tension from the formation of an hæmatoma. Bleeding from a tooth socket is consequently especially fatal.

This hæmorrhage produces anæmia and in consequence weakens the patient and if blood clot is allowed to become septic in the mouth or intestinal canal there is further risk to the patient's health and particularly to his happiness. Fortunately the occurrence of a hæmorrhage is followed after a time by an increased coagulability of the blood so that the hæmorrhage is less likely to be repeated for a while until the condition of the patient is somewhat improved.

Eventually, however, another hæmorrhage occurs and after that another until the patient dies from exhaustion or from actual loss of blood.

In some cases, especially those which have not been apparent until adult life, and in some females of hæmophilic families there is a less persistent tendency to bleed and the hæmorrhages may after a while disappear.

In other cases the hæmorrhages from mucous membranes, etc., are the less prominent part of the disease, their place being taken by effusions into joints. These in time lead to ankylosis of the joints affected and so render the patient a cripple. He may outlive the hæmophilic tendency but the ankylosis remains as the last chapter in the pathology of the disease in his case.

Thus the pathology of hæmophilia is very simple after a certain point. Hæmorrhage, repeated hæmorrhage, exhaustion, death, or recovery with ankylosed joints sums up all we really know of the condition clinically and apart from the laboratory.

Etiology.—Nothing is known of this beyond the hereditary factor. Briefly stated this amounts to the fact that unaffected females transmit the disease to some of their male children but not to all, whereas to their daughters they transmit a potentiality of handing on the disease. The females of affected families may show signs of the disease in the shape of hæmorrhages but this is not often the case—more rarely still they show all the signs of the disease. The disease has apparently been transmitted in rare instances by males but this must be very exceptional and such cases ought to be very carefully recorded if they are to be accepted. This has so seldom been the case that the matter must be regarded as to some extent still undecided.

There would appear to be some families in which both sexes participate in and transmit the disease in fairly equal proportions.

Actual hæmorrhage may certainly follow a slight trauma but in many instances there is no proof of even the smallest injury.

General ill health or specific diseases may cause a recrudescence of the symptoms when they have been for a long while in abeyance.

Age.—The disease is usually first noticed in early childhood and is then more severe than when it has been absent as far as we can tell from the symptoms until adult life. It seems, therefore, to be a disease especially of childhood.

Onset.—The onset is usually with either an effusion or a hæmorrhage. Prodromal symptoms in the shape of malaise, puffiness of the face and of the joints have been noted but these are more apt to precede the periodical exacerbations of the disease than the onset of the disease itself—which is congenital in the great majority of cases.

General Symptomatology.—The subcutaneous hæmorrhages are often associated with swelling but may also appear merely as bruises. They are painful and tender. They resolve like other hæmorrhages—sometimes they are at once seen not to be true hæmorrhages by their light tint showing that there is a greater proportion of serum than of corpuscles in the effusion.

Spontaneous hæmorrhages usually occur from mucous membranes especially from the nose. When the mouth is filled with blood and constant oozing renders it almost impossible to keep it clean the supervention of sepsis is almost certain and is both dangerous and unpleasant. The same may be said of intestinal hæmorrhages which form a good nidus for micro-organisms. Otherwise hæmorrhages do not give rise to other symptoms than those of loss of blood. They are especially apt to occur at night and a small abrasion that has not bled during the day may bleed profusely at night. This bleeding may occur when the patient is asleep and prove all the more serious from this fact—a very great deal of blood may be lost before steps are taken to stop the hæmorrhage.

The effusions into joints are the next in importance of the symptoms of hæmophilia. These do not as a rule occur until the joints bear the weight of the body and tend to vanish as the patient comes to adult life. The effusions do not always nor even often entirely subside and what is left may organise and lead to fixation of the joints—usually the large joints are affected. An osteo-arthritis may follow with extreme degenerative changes, lipping of the bones, erosion of cartilage and absorption of bone.

These are the most characteristic symptoms of hæmophilia but there are certain other points which may be mentioned. In a fair number of cases a depraved appetite has been a prominent feature—as it is in many cases of chlorosis. Some of the patients might even be said to be such as would welcome the state of affairs hinted at by the poet—

> "Chalk and alum and plaster are sold to the poor for bread."

It is particularly such articles as those mentioned that are eaten.

Pyorrhœa alveolaris seems to be of very common occurrence and is a serious factor as it provides many opportunities of abrasion of the mucous membrane. Chilblains and urticaria have been noted as frequent accompaniments of the disease.

The tendency to bleeding is not at the same level throughout the disease and this is not entirely accounted for by the increase in the coagulability of the blood which follows a hæmorrhage. Exacerbations can sometimes be foretold by the patient and are not very rarely accompanied by nervous symptoms such as increased irritability or even a stuporose state. Headache may then accompany the attacks and this may be due to serous effusion into the central nervous system.

Diagnosis.—Family predisposition is undoubtedly of the first importance and is to be carefully enquired for. In its absence it may be almost impossible to make a sure diagnosis. This is especially likely to be the case if the joints bear the brunt of the disease and are complained of by the patient. Purpura is almost impossible to distinguish except that in the latter condition it is very rare to find single hæmorrhages. An examination of the coagulability of the blood is of assistance and as there is often a diminution of polymorph leucocytes this also may be of some diagnostic significance. If the blood be examined too soon after a hæmorrhage there may be increased coagulability and increased polymorphs so that examination should be deferred for a week. The type of anæmia will not give any assistance. It is merely that of any anæmia following hæmorrhage.

Treatment.—Persons who are members of a family in which the hæmophilic tendency has been noted ought only to marry with the full knowledge that they may be transmitting the disease. This applies to both males and females although in the former case the absence of any male transmission in the family may be held sufficient justification for marriage.

All such persons should be carefully guarded from trauma in their childhood and should be informed of the family tendency as soon as they are able to comprehend it in order that they may acquaint dentists and doctors with the fact in case of any operation being contemplated.

Trauma is not infrequent at schools—both judicial and accidental. The hæmophiliac has in regard to the former a slight advantage over his fellows—the only one he is likely to have.

We know of no means of preventing the transmission of the disease except by the avoidance of conception. No drug is of avail. In individual cases something may be done by the administration of calcium salts. Ten grains of calcium chloride or lactate may be given daily to an adult and less to a child in proportion to the age. As long as this is continued there will probably be a lessened tendency to hæmorrhages although it cannot be said that they will be prevented.

In the presence of a hæmorrhage which requires stopping a larger dose of calcium must be given, *e.g.*, twenty grains and this be repeated every day until the hæmorrhage shows signs of stopping or until other steps can be taken. Hæmophiliacs should have some doses of calcium handy at all times.

There are various steps which may be taken to deal with the hæmorrhage locally but there are also other internal medicines which may be given and which have been strongly recommended. These are extracts of the thymus gland which can be obtained in tablet form of five grains each. These may be given up to ten or twelve a day. The administration of CO_2 has been advocated but is unfortunately not a very practicable measure in many cases. It certainly increases the coagulability of the blood in vitro and has proved of use in practice. It may be generated from a Kipps apparatus and passed through water. It should be either given with oxygen or in so small a stream that the respirations are not deepened.

An extract of thymus gland or testis makes a very good local application, being a very powerful styptic. It is made by extracting the gland with normal saline solution to which is added 0.5 per cent. of calcium chloride and 1.0 per cent. of carbolic acid.

Injections of serum have been employed but they are open to the objection that we know too little of anaphylaxis and the symptoms which may follow repetition of the injection to use it in cases where such repetition is almost certain to be required.

In some cases lesser measures may suffice such as pressure or the application of adrenalin, etc. (see page 338). Freezing a tooth socket with ethyl chloride spray has been advocated and might well be of use.

The joint changes are very difficult to deal with especially if they are already advanced when first seen. Where possible every attempt should be made to prevent ankylosis with consequent atrophy of muscles and further joint changes. Forcible movements are open to the objection that they may cause further effusion and this objection would appear to be valid unless there is evidence that the hæmophilic tendency is dying out in the individual under treatment. For acute effusions rest must be enjoined and early passive movement and massage. The chief danger arises when the weight of the body is again borne on the legs or if there is any intercurrent disease.

In spite of treatment many of these patients become crippled for life if they do not die of hæmorrhage before the joint changes are sufficiently advanced to cripple them.

THE HÆMORRHAGIC DISEASE OF THE NEW BORN OR HÆMOPHILIA NEONATORUM

It sometimes happens that new born children suffer from a form of hæmorrhage which seems entitled to consideration as the out-standing symptom of a clinical entity. These hæmorrhages may be from the umbilical cord, the stomach or the bowel. They are profuse and death usually occurs unless treatment is prompt. Hæmorrhage does not occur until at least thirty hours after birth as a rule. There is said to be a lessened coagulability of the blood but the chief practical point is the question of treatment.

Treatment should as a rule consist of more than the usual measures for stopping hæmorrhage and the use of serum has been found very advantageous and has given the best results so far of any treatment tried. In one case in which it was not successful transfusion led to a period of freedom from hæmorrhage but did not avert a fatal result. As a rule the tendency to hæmorrhage once held in check for a few days does not recur. There is no family history of hæmophilia. The dose of serum, etc., is given on page 338.

CHAPTER XIX

PURPURA

Purpura is the name given to a symptom which is not uncommon in the course of the diseases commonly called blood diseases. It is used to designate the occurrence of hæmorrhages under the skin—these may be appreciable clinically as red spots or as bruises. In either case the various colours associated with a bruise are seen later. With purpura there are often found hæmorrhages in other situations especially on the surface of organs covered by a synovial membrane such as the lungs, viscera, etc. There may also be profuse hæmorrhage from mucous membranes. In fact, the consideration of purpura entails a consideration of all hæmorrhages not apparently due to trauma or any preexisting lesion.

These hæmorrhages may consist of blood or of serum in which there is not the full complement of corpuscles.

It is obvious that in the latter case there has been no true hæmorrhage but merely diapedesis from the capillaries. Such hæmorrhages are apparently very rare and have been called serous hæmorrhages. They are met with in hæmophilia and rarely in other conditions. They may be associated with urticaria.

The ordinary hæmorrhages of purpura seem to be due to actual rupture of vessels. In a case of severe anæmia in which hæmorrhage under the skin has not occurred it may sometimes be induced by raising the blood pressure locally with a constricting bandage. This suggests that the walls of the capillaries are weakened and give way on the application of pressure from within. The fact that fatty degeneration is a well-known symptom of anæmia and is especially apt to affect the vessels is further evidence in favour of a "burst vessel" theory of purpura. The further fact that purpuric spots are especially found on unsupported serous membranes bears out the theory. Hæmorrhage, for instance, into a muscle where the vessels are well supported by the surrounding tissues is extremely rare.

If then purpura be the result of either weakened walls or raised blood pressure we should expect to find it in a great number of conditions. This is the fact but it is seldom that it can be attributed to raised pressure acting on normal walls. Nevertheless, the epistaxis of Bright's disease may be supposed to be an example of this although the vessels are hardly perfect in that condition as a rule.

Purpura is commonest in septic conditions and in anæmia. These are both conditions in which fatty degeneration is common.

We may then consider for practical purposes that purpura means fatty degeneration of the vessels in the great majority of cases, but that in a few it depends on diapedesis of the blood cells and that the latter class of case is not at present explicable.

The clinical subdivisions of purpura are not with the scope of this volume, for purpura is essentially a symptom and not a disease and many of the morbid processes with which it is associated are in no way germane to a volume which deals with hæmatology.

PURPURA HÆMORRHAGICA

This may occur as a sequel to acute infective disorder or may occur as an apparently idiopathic clinical entity.

The disease consists of profuse and widespread hæmorrhages under the skin and from mucous membranes and is accompanied by the general symptoms of an acute infective disorder. It is commonest in children.

The blood shows secondary anæmia of the post-hæmorrhagic type.

It is very doubtful whether this be a specific disease. It is dealt with in text-books of medicine.

There is no specific treatment, but serum is of great value.

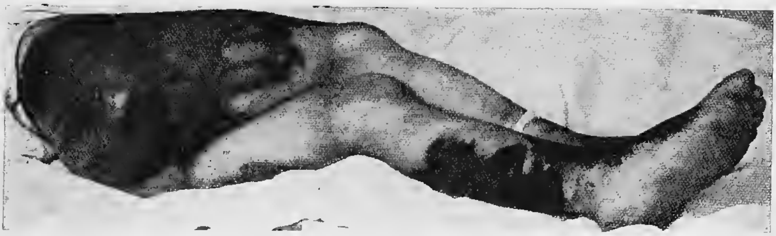


FIG. 40.—Extensive purpuric ecchymosis. (By kind permission of Drs. Rolleston and McCririck.)

CHAPTER XX

LEUKANÆMIA

This term has been used as descriptive of a disease the diagnosis of which rests solely on a blood picture. The blood picture in question shows changes in the red cells similar to those met with in Addisonian anæmia and a hint of the changes in the white cells which are characteristic of myelæmia. Were this hint accentuated into a satisfactorily large leucocytosis, *e.g.*, 300,000 per c.m.m. the diagnosis of myelæmia would be clear enough for the red-cell changes are common enough in the latter disease. We have seen elsewhere that the number of leucocytes is not nearly so valuable a sign of myelæmia as is their nature (with the reservation that a very large leucocytosis relieves us of the necessity of looking further) and there is nothing in the recorded cases of leukanæmia to prevent them being attributed to myelæmia in which the blood picture is atypical.

One case perhaps was Addisonian anæmia with an unusual number of myelocytes—which are almost constantly present in some degree in the late stages of that condition—but the others seem to have all been cases of leukæmia and the clinical signs bore out such a diagnosis as much as the blood picture.

The mere fact that this term, leukanæmia, should ever have been coined shows the danger of basing the diagnosis of a disease on the blood picture. Blood examination is a good servant but a very bad master. It is true that we can sometimes unhesitatingly diagnose a disease from a blood examination but there is no condition of the blood which necessarily excludes either leukæmia or Addisonian anæmia, however rare the atypical cases may be.

The so-called blood diseases are almost all disease of the bone marrow or lymph glands and it is not essential for this disease to be at all times reflected in the blood stream.

The term leukanæmia and all its works should be avoided. It connotes no definite clinical condition nor even a constant blood picture.

CHAPTER XXI

THE BLOOD IN SURGICAL DIAGNOSIS

Certain aspects of the general diseases of the blood-forming organs are likely to come under the notice of the surgeon. Unless they come with a ready-made and correct diagnosis there is grave danger of the diagnosis being missed, for it is as a rule only the most uncommon and puzzling features that seem to call for surgical interference. Thus the glandular enlargement of Hodgkin's disease will give no trouble, for this is one of the causes of "glands" that will naturally be excluded. But an abdominal tumour in the same disease and caused not by splenomegaly but by a mass of mesenteric glands may give rise to great difficulty in diagnosis. In this case the surgeon would probably explore the abdomen and this procedure would not necessarily have been contra-indicated if the diagnosis had been apparent, for surgical assistance can often give great relief in Hodgkin's disease. With a case of lymphæmia which might present exactly the same features at the bedside, exploration would very likely prove fatal. It has been done on more than one occasion and as far as the author can discover always with a fatal effect.

The obvious inference is that with a case of hidden tumour such as an abdominal tumour a blood count is always advisable whatever the clinical features of the disease may be.

This inference is strengthened when we consider the other tumour formations which may be met with in leukæmia. As has been already noted not only may lymphatic tissues whereever situated be enlarged but even in situations from which lymphatic tissue is commonly supposed to be absent there may be large growths. A brief enumeration of some of the operations which have been actually performed will assist toward an appreciation of the extraordinary difficulties in diagnosis which may arise. They include amputation of both breasts (two cases), excision of the upper jaw, complete mastoid operation, numberless excisions of tumours of the skin, laparotomies, etc. In each case there was present a tumour which seemed to demand operative measures but which would probably have been left alone if its true nature could have been ascertained—as it might have been in these cases by a blood examination.

It may therefore be said that in the case of an apparent sarcoma—carcinoma is seldom simulated—examination of the blood may be of great value and that in the case of multiple sarcomata it should not be omitted if facilities for its performance exist or can be procured.

In addition it may be pointed out that if an individual show enlargement of the spleen and lymph glands or of the spleen and liver or of spleen, lymph glands and liver together there is a prima facie case for blood examination before surgical treatment is undertaken for the enlargement or for any concomitant condition.

The severer anæmias do not very often come under the notice of the surgeon but it does occasionally happen that the diagnosis as between cancer (especially of the stomach) and "pernicious" anæmia is in doubt. If there is in such a case an absolute or relative leucocytosis the diagnosis of cancer is almost assured—a leucocytosis in "pernicious" anæmia is extremely rare and then only occurs as a symptom of some obvious complication.

The surgeon's attention will not as a rule be directed to any of the other diseases dealt with in the preceding pages except that he may be called in to deal with hæmorrhage. The blood diseases will therefore not be again mentioned.

The presence or absence of a leucocytosis is often of great moment to the surgeon for it is one of the most valuable signs in differentiating benign from malignant growths, infective from other disorders and appendicitis from typhoid fever. That is to say, it becomes very valuable when the clinical signs are equivocal—no one would pretend that an examination of the blood can take the place of careful clinical observation.

The leucopenia of typhoid fever (*q.v.*, page 382) is early and constant, the leucocytosis of appendicitis is not so early inasmuch as it is not likely to be at all well marked until pus forms. A single drop of pus, however, may cause a leucocytosis of 40,000. In a catarrhal appendicitis there may be no leucocytosis but there is no leucopenia so that the differentiation is still easy.

In any case when the surgeon has reason to suspect pus formation a blood examination may be of great value for leucocytosis of a high grade (30,000–50,000 or above) more often indicates pus formation in surgical practice than anything else. It is, however, necessary to exclude lobar pneumonia and acute rheumatism—which is seldom difficult although the former may give trouble in children.

Leucocytosis does not occur as the consequence of the presence in the body of a benign tumour unless that give rise to some complication such as intestinal obstruction or volvulus. It is frequent but not constant with malignant tumours. Therefore when the nature of a tumour is in doubt the absence of a leucocytosis is of no particular assistance but its presence excludes benign tumour. Even if there is no leucocytosis there is a further test which may be applied and is sometimes of assistance. This is the iodophil reaction. It is performed by exposing a dried but unfixed blood film to the vapour arising from iodine crystals in some closed jar for about half an hour. The film is then examined with the oil immersion and there may be seen in some of the leucocytes (the majority of which stain light yellow or not at all) a brownish discolouration or brown granules. This may be taken as a postiive proof of some organic disease, *e.g.*, it renders the diagnosis of "functional" untenable and is therefore of value in some cases. It occurs also in insanity but not in hysteria.

An eosinophil leucocytosis is chiefly of value to the surgeon in cases of cysts of doubtful origin. It is invariable with hydatid cyst if the latter be living. With a suppurating cyst it may disappear and also with an old calcified one. Even in these cases it is sometimes present. In countries in which hydatid cyst is of common occurrence a doubtful cyst is considered an hydatid until operation proves the opposite. In other countries the hydatid is less commonly thought of in the first place. Hence the use of a blood examination. A cystic growth accompanied by eosinophilia is almost certainly a hydatid.

Eosinophilia is also met with in cases of helminthiasis and may on occasion be of use to the surgeon in this connection.

CHAPTER XXII

METHODS OF TREATMENT

MEDICAL TREATMENT OF HÆMORRHAGE

Hæmorrhage is a common feature of blood disorders and is always a serious factor. Moreover hæmorrhage once started often shows an unwillingness to stop until the patient has almost bled to death. This is chiefly the case in hæmophilia but may also occur in other blood diseases. Treatment of this symptom is accordingly a very important branch of therapeutics.

The subjoined account epitomises some of the methods which have met with most success.

There are two divisions of the subject according as the hæmorrhage can or cannot be treated locally. We will deal first with hidden hæmorrhage—concealed hæmorrhage would be a better phrase but this has been appropriated by the gynecologists.

Opium holds the first place for many reasons and perhaps chiefly because it calms the patient while it exercises a beneficial effect on the hæmorrhage. It is best given hypodermically since the quickest possible result is usually required. The dose is the usual 1/8–1/4 gr. Unfortunately opium although excellent for other reasons has no very marked effect on the hæmorrhage itself in the ordinary doses.

Recently the use of serum has been much advocated and apparently with good reason—especially in the treatment of hæmophilia neonatorum. Human serum is the best and safest and is easily obtained. Blood should be drawn from a vein at the bend of the elbow through an ordinary aspirating needle which conducts it through a short piece of sterilised rubber tubing to a sterilised flask. It is allowed to coagulate and the serum is then ready for use. If the arm be constricted above the site of venipuncture a vein will be rendered prominent and can easily be pierced in a slanting direction (to prevent transfixing the vein) when the blood will flow of its own accord until a considerable amount has been collected. In the case of children 10 c.c. can be given three times a day but larger doses can be used with no ill effect—in fact with good effect as the serum is a food stuff of considerable value. It is given subcutaneously and is quickly absorbed. The question of anaphylaxis does not arise when human serum is used.

If human serum cannot be obtained, although this should not prove difficult when the life of a child is in danger and there is a healthy parent about, it is permissible to use anti-diphtheritic serum or anti-streptococcal—in fact, any sort of serum that may be available of the common antitoxic varieties. Most of these consist of horse serum—the presence of a specific antitoxin is of no importance. In these cases symptoms of the serum sickness may be expected in a minority of cases. These are urticaria, fever, etc. Not only is a first dose of serum toxic of itself (although seldom if ever fatal) but it sensitises the patient so that a second dose is far more dangerous. Even then in the majority of cases no untoward happening is noted but in a few sudden death has occurred.

It is only fair to state that there is still considerable difference about the efficacy of this, one of the latest methods of treatment but it would seem to have a good deal to support it and should be tried especially in hæmophilia neonatorum.

Transfusion has been tried in a certain number of cases of hæmorrhagic disease and in some has been quite successful. It would appear very probable that these good results were really due to the incidental dose of normal human serum. The whole question of transfusion is dealt with on page 343.

The administration of salts of calcium has also been very extensively tried of recent years and the reports are distinctly conflicting. The author's feeling on the subject is that as a prophylactic calcium is often of distinct value but that as a treatment for an existing hæmorrhage nothing very striking is to be expected to follow its administration. Calcium is deficient in the blood in certain conditions but we cannot tell except by experiment whether any given case shows a deficiency or not. The method of calcium estimation introduced by Blair Bell does not estimate all the calcium and is a little involved for general use. It is therefore not at present adapted for extensive clinical use although the administration of calcium carefully checked by this method has been productive of some interesting results in the author's hands. Calcium lactate is a convenient salt to use and may be given in 10-grain doses three times a day to an adult. This is a prophylactic dose and for actual hæmorrhage the same amount may be given every four hours. In any case the result is the best guidance to the dosage. If the coagulation of the blood is hastened the calcium is doing good.

A rough but clinically convenient method of estimating the coagulation time is as follows:

A prick is made in the ear as for an ordinary blood examination and the first drop of blood wiped away. As soon as the next drop exudes an assistant notes the time or if a stop watch is available sets it going. At half-minute intervals a fine needle is passed through the drop of blood which has been caught on a glass slide (as if for spreading) and when it picks up a thin thread of fibrin the time is again noted. The time which has elapsed from the exuding of the drop to the appearance of the fibrin thread is the coagulation time of the blood. This method gives results which are of value for purposes of comparison but are not necessarily correct measures of the actual coagulation time.

Calcium salts should not be given subcutaneously as they are very apt to cause necrosis.

Adrenalin has been given hypodermically for hæmorrhage. It is not to be recommended. Gelatin in 5 per cent. solution has been given subcutaneously and also by the mouth. In a few cases it seems to have been followed by cessation of hæmorrhage and is among the drugs which may be tried. The subcutaneous method is attended by the danger of tetanus supervening as one can seldom be certain that gelatin has been adequately sterilised. It has also been applied on gauze to external hæmorrhages but the same risk attaches.

There is perhaps no more distressing sight to the physician than that of a patient bleeding to death from a continued hæmorrhage which all means have proved powerless to check. The present writer remembers such a case in which the hæmorrhage was eventually held in check by a remedy which is perhaps little used nowadays, viz., oil of turpentine. This may be given by the mouth in 20-minim doses every four hours until the hæmorrhage ceases. It should be given as an emulsion with tragacanth or something similar. Terebene in the same dose has the same action and is more pleasant to take. This is a very powerful remedy but the danger of toxic symptoms, especially nephritis, is considerable.

Almost all the astringent drugs have been used internally as well as externally for hæmorrhage and in some cases have proved very efficient. They may naturally be expected to benefit some cases of hæmorrhage into the alimentary tract but are then to be regarded as local applications.

Wright has recommended the use of carbon dioxide gas by inhalation since this gas is known to increase the coagulation of the blood, or, to put it another way, venous blood coagulates more readily than arterial in virtue of its greater CO_2 content. He generates the CO_2 in an ordinary Kipps apparatus at the bedside. Apparently the administration can be continued for half an hour at a time but the stream of gas should be so small that there is no deepening of the respiratory movements. The writer has no experience of this method which is recommended for hæmophilia.

The treatment of hæmorrhages which can be seen and to which local applications are possible is usually less difficult—surgical measures such as pressure being first tried. In practice these hæmorrhages are of few varieties and perhaps that from a tooth socket is one of the most frequent sources of trouble. It is true that this source of hæmorrhage is not especially common in the blood diseases with the exception of hæmophilia but it may be met with and merits remark. Pressure is usually applied in the first place by plugging the tooth socket and this is not infrequently sufficient. It is, however, difficult to keep the plug in position. It should be made big enough for the patient to bite on and a jaw bandage will often impress on the patient the importance of keeping the mouth closed. The plug may be soaked in various substances of which adrenalin is one of the most used. The author prefers to use hydrogen peroxide on iodoform gauze when possible. It is true that this gives rise to a good deal of effusion frothing in the mouth and is not exactly an elegant practice but this seldom proves a drawback in practice as the patient is only too willing to adopt any measure that is of use. If this does not stop the hæmorrhage the actual cautery may be employed but is not pleasant and is contra-indicated in hæmophilia if not in other blood diseases. Stitching the gums together over the socket has also been advocated but neither of these last two measures are at all likely to prove acceptable to the patient unless he is very frightened. A writer in the Lancet some years back advocated freezing the tooth socket with ethyl chloride. This would certainly tend to close the mouths of the vessels and if they did not open again with the subsequent reaction might be very useful. The writer in question said that it had been very successful in his own practice.

Epistaxis as is well known is very often due to hæmorrhage from a spot on the anterior part of the septum which is easily reached, but there are many cases in which the hæmorrhage comes from the back of the nose and is not easy to deal with. Plugging with gauze soaked in hydrogen peroxide, adrenalin, ferri perchlor, etc., may stop it but, on the whole, in blood diseases it is better to treat it as a hidden hæmorrhage and administer one of the drugs above mentioned for internal use.

For the general oozing from the gums which is so common in terminal stages of leukæmia the author knows of no better remedy than hydrogen peroxide which is at once a styptic and a non-irritant antiseptic. It will often effect a wonderful improvement in the condition of the mouth. It may be followed by glycothymoline or some similar preparation to remove the unpleasant taste. The usual strength of hydrogen peroxide is 20 volumes, *i.e.*, one volume of the fluid gives off 20 volumes of oxygen. This may be used in 25 per cent. solution or at full strength if the mouth is not very septic and the gums softened, for example, when a tooth socket is being dealt with.

Finally it should be mentioned that when there is a tendency to hæmorrhage pressure will often cause subcutaneous ecchymoses. This is so not only in the blood diseases but also in the severe cases of acute specific fevers. Experimentally this has been seen to be due to increased local congestion—or peripheral conjestion if for example a bandage be applied to a limb. This therefore is to be avoided and even fomentations may be productive of considerable bruising over the area to which they were applied.

TRANSFUSION

Transfusion has been practised for many years and the results have been conflicting almost from the first. Some of the earliest experiments were witnessed by Samuel Pepys at Gresham College where he saw "a pretty experiment of the blood of one dog let out, till he died, into the body of another on one side, while all his own ran out on the other side." It appears that "the first died upon the place, and the other very well, and likely to do well." He remarks that the transfusion of blood "may if it takes, be of mighty use to man's health, for the amending of bad blood by borrowing from a better body." Later an experiment was performed on a man "that is a little frantic, that hath been a kind of minister, that is poor and a debauched man, that the college have hired for 20 s. to have some of the blood of a sheep let into his body."

The experiment was performed and the poor and debauched man, in spite of his character, seems to have stood it very well, for he later gave an account of it in Latin in which he said that he had distinctly benefited or, as Pepys puts it "that he finds himself much better since and as a new man, but he is cracked a little in his head though he speaks very reasonable and very well. He had but 20 s. for his suffering it and is to have the same again tried upon him; the first sound man that ever had it tried on him in England and but one that we hear of in France which was a porter hired by the virtuosos."

From this time (1667) onward the practice of transfusion has been praised by some and condemned by others and perhaps the truth of the matter may be deduced from some of the following facts. It is known that injections of serum (which are naturally incidental to transfusion) are of benefit both as providing food and as tending to stop hæmorrhages. It is also known that hæmolysis may occur and prove fatal to the patient. Further anaphylaxis may have a similar fatal issue and may be absent on a first injection and very marked on a second. But although this may occur it does not always do so and is not to be expected when the donor and the recipient are both of the same species. Lastly there is every reason to suppose that the products of blood destruction within the body are the best stimulants of blood regeneration so that benefit may well be expected to accrue from transfusion on these grounds alone.

From these facts we should expect to find, as we do, that the results of transfusion performed in a more or less haphazard fashion would be very confusing. Those cases in which death followed transfusion very shortly may have been instances of anaphylactic shock. Those in which transfusion was of great benefit may well have been among the lucky ones who were able to survive the immediate effects and to benefit in consequence.

The indications for transfusion would seem to be very few, especially as saline infusion will do so much to combat the shock of many of the conditions for which it has been performed, *e.g.*, for profuse hæmorrhage. As there is no lack of blood-forming energy in these cases transfusion would only be indicated when saline infusion had failed. It might be given then on the supposition which is neither proved nor disproved that the red cells of the donor can act for a while at least as oxygen carriers in the blood of the recipient.

Even in such a case experiments ought to be made beforehand to exclude the presence in the donor's serum of agglutinins or hæmolysins for the patient's corpuscles.

Finally one can but conclude that the only application of transfusion which rests on a more or less satisfactory theoretical basis is that which has been least practised, viz., the intravenous administration of very small quantities of red cell suspensions. These are given in order that they may be destroyed and so stimulate the marrow to further activity. There may be symptoms of shock, sweating, fever, etc., but these are of short duration. The injections, *e.g.*, of 1 c.c. of a 25 per cent. emulsion may be repeated every four days or so until distinct improvement is shewn. A blood crisis following such injections is frequently noted.

Except in the above modification one can see but little chance of the prohibitive dangers of transfusion being removed for some years, until, in fact, knowledge of the properties of the blood plasma is much more extensive than at present.

THE EMPLOYMENT OF X-RAYS

In the main this is a matter for the expert in the use of the rays and most matters of technique are best left to him and will not be dealt with here.

X-rays are most used in leukæmia of either type, in other diseases in which splenomegaly is a feature and in lymphatism.

It is important to remember that the action of the rays if too long continued is directly destructive to tissues. Ordinarily they probably act indirectly by stimulating the resistance of the body rather than by destroying the abnormal tissues, *e.g.*, the marrow overgrowth in myelæmia. It is this effect that is desired and the further destructive effect is dangerous. The following statements must always be read with this idea in mind.

It has been a general practice to apply the X-rays where there is glandular enlargement over the enlarged glands and where there is splenomegaly over the spleen. It is improbable that there is any direct advantage in so doing and as a rule application of the rays to any other part of the body has the same effect. In myelæmia with greatly enlarged spleen the rays may be conveniently applied over the lower parts of the femora and to the ribs on alternate sittings. If it is also desired to apply them to the spleen no harm is often done. By thus varying the spot at which the rays are applied there is less risk of causing injury to the skin.

The applications should not be too long, 30 minutes is the most which should be used at a time, and at the commencement not more than ten minutes should be tried.

This can be repeated every third or fourth day and continued so long as the blood changes seem to warrant it and, in glandular diseases without blood changes, until the glands are very sensibly reduced. Sittings should then be less frequent, *e.g.*, once a week and later still once a month. At the end of a period not longer than three months the patient will probably express himself as being better than he has been for years. This is a danger signal; a sign that he feels himself cured and will probably drift out of sight. As a matter of fact he is not cured and, although the treatment may have given him so much as three clear years of health, he will inevitably relapse. It is therefore of the first importance that patients should be instructed to report themselves from time to time for examination and, if necessary, for further treatment.

In cases of lymphatism in young children, especially where the thymus is enlarged and has been giving rise to attacks of dyspnœa, the treatment may be permanently successful for it will enable the patient to tide over the period during which lymphoid tissue normally tends to be in excess and reach the safety of a period in which the tissues are differently balanced, *i.e.*, adult life. In cases of lymphatism in adults the issue is not so certain. The disease is, however, very seldom diagnosed in adults until after death.

In cases of leukæmia in which the result of treatment can be accurately followed by examination of the blood, this should be undertaken between every separate treatment. The white cells should not be reduced too quickly—a steady reduction of a few thousands a time is better than a large fall of sudden occurrence. But the white cells although an index of treatment do not afford so good a means of estimating the possible dangers as do the red cells. As is well known the action of the rays on the red-cell-forming tissues is such as to destroy them and this is shewn in the circulating blood by the increase of a pre-existing anæmia or by the development of a deficiency of red cells during treatment.

When this occurs treatment must be suspended—provided of course that the anæmia cannot be reasonably considered due to hæmorrhage or other known factors. It is also an indication to cease applying the rays over the active blood-forming areas, *e.g.*, the ribs.

There are few physical signs of an overdose of X-rays but there is not very infrequently an extensive skin eruption which is considered to be due to the sudden destruction of white cells in some cases and which takes the form of general erythema, with irritation and often desquamation.

There may also be an increase of the nitrogenous derivatives in the urine and an unusually copious deposit of urates or uric acid (there is normally excess of these in leukæmia) should suggest caution.

THE ADMINISTRATION OF ARSENIC

The available and useful preparations of arsenic are far fewer in number than those of iron. They are:

Liq. Arsenicalis	2–8 m.	1–5 dmils
Liquor Arsenici Hydrochloricus	2–8 m.	1–5 dmils
Liquor Arsenii et Hydrarg. Iodidi	5–20 m.	3–12 dmils
Atoxyl, and its allies.		
Salvarsan, and its allies.		
Those compounds of iron and arsenic mentioned later.		

Of these the first two are the most useful and for general purposes Liquor Arsenici Hydrochloricus is to be preferred. It can be combined with Liq. Strychninæ without danger whereas Liq. Arsenicalis is not compatible. The dose given above is small compared with what it may be necessary to give, but 3 minims is the best dose to start on and 8 minims is much too much at first. From 3 minims the dose may mount to 1/2 drachm by 3-minim increments or even higher—it must always depend on the reaction of the patient. Particular attention should be paid to signs of arsenic poisoning (see below).

Atoxyl is a trade name for a combination of arsenic with carbon, *i.e.*, an organic combination of arsenic. The arsenic ion is inactive while it remains in this combination but is liberated by the oxidising agency of the body tissues. It is then extremely active and dangerous—it is impossible to say how much active arsenic will be liberated or what its effect may be. For many thousands of cases in which this drug has been given there may have been relatively few mishaps but this does not alter the fact that there have been sufficient to render the use of this preparation very inadvisable—at least as far as the hæmatologist is concerned.

Salvarsan has all the advantages, if any, of atoxyl and is better under control. It has been used in most blood diseases in which arsenic is given and is as useful as the simpler forms. The question of whether it may not be better has been answered in different ways and on the whole the writer sees no cause at present for a more general use of the drug in blood diseases. Liq. Arsenicalis Hydchl. is as useful and less liable to untoward developments. It is also cheaper to administer since salvarsan in the hands of those who do not thoroughly understand the technique of administration is as dangerous as atoxyl.

The combinations of arsenic and iron suitable for hypodermic administration are given on page 355.

Symptoms of Arsenical Poisoning.—The hæmatologist is almost entirely concerned with chronic arsenical poisoning and of this there are three chief symptoms. The first is a brownish pigmentation of the skin, usually with some desquamation, and affecting all parts of the body. The flexures of the joints may be more affected than other parts and the oral mucous membranes usually escape. Such pigmentation is occasionally met with as part of various blood diseases, *e.g.*, in Addisonian anæmia, and then confusion may arise. It is better if arsenic has been extensively used to consider it due to arsenic and consequently exercise care in the use of this drug. The pigmentation itself is harmless although disfiguring. The later effects of arsenic on the skin may be more dangerous. These are thickening of the skin on the palms of the hands and soles of the feet with, in some cases, small "corns" The latter tend to become epitheliomatous.

It may be noted that the pigmentation of the skin seen in some cases of Gaucher splenomegaly and in early cases of hæmochromatosis is apt to be confined to the face and hands and, in the latter case, is situated chiefly about the hair follicles.

Dermatitis and almost every possible variety of skin lesion may be met with, apparently in relation to the administration of arsenic, but is uncommon. If there is a pre-existing skin lesion it may be aggravated. Herpes zoster may be met with.

Peripheral neuritis is a well-known result of the administration of arsenic for long periods. It does not exhibit any particular affinity for the upper or lower limbs but attacks them impartially. In this it differs to some extent from lead and alcohol. The paresis clears up if the drug be not continued but only rather slowly.

Intestinal disturbances, such as gastritis and enteritis, are often difficult to ascribe without doubt to the arsenic since they are not uncommon accompaniments of the diseases for which arsenic is largely given. The trouble arises chiefly in Addisonian anæmia and as a rule it is not the arsenic but the disease which is responsible and there is no need to withhold arsenic.

Very chronic arsenic poisoning sometimes shows itself in the form of thickening of the colon—often with necrosis of the superficial layers. This is seldom detected during life and probably never diagnosed.

Acute arsenical poisoning may occur after the administration of salvarsan. The symptoms vary but diarrhœa is common and there is always considerable shock. Fortunately this may pass off very quickly.

Sudden blindness has followed the use of atoxyl and its allies and for this reason they have been largely given up—except for the treatment of diseases which do not come within the scope of this volume such as sleeping sickness.

THE ADMINISTRATION OF IRON

Iron is one of the drugs which is constantly prescribed in anæmia and the number of preparations, official and unofficial, is very great. Many of them, however, are really unnecessary.

For use as a styptic the Liquor Ferri Perchlor. is as useful as any but, although not lacking in power in the matter of controlling hæmorrhage, is not at all an "elegant" preparation. It is often difficult to remove if that is necessary owing to its having failed to stop the bleeding and it also makes a most unsightly black mass about the bleeding point. It is used as a rule for hæmorrhage from more or less visible spots and is applied on lint or gauze soaked in the preparation.

It may also be used, diluted with one part of water, for a vaginal douche or rectal enema but should not be introduced into the uterus.

It cannot be given internally in doses which would be sufficient to stop hæmorrhage, *e.g.*, from the stomach, without causing gastro-intestinal symptoms.

The tincture is of the same value in similar circumstances. Either of the drugs should only be used as hæmostatics when nothing else is available or when other measures have failed.

The only other external use of iron which seems to have been at all recognised is inunction. There is little if anything to recommend this. Hæmoglobin inunctions have also been employed. If it is desired to give iron and it is not tolerated by the stomach it can be conveniently given as an intramuscular injection; the technique for the latter is given below.

Iron is in the great majority of cases given by the mouth and it is not now considered necessary that the patient should undergo some sort of preparation before taking iron. The objection is sometimes raised that it blackens the teeth and in such case it may be given in the form of a pill or as the peptonate solution.

Where there is gastric disturbance when it is desired to commence the giving of iron, it is well to use a mild and non-irritating preparation. The scale preparations, viz., Ferri et Ammon. Cit., Ferri et Quin. Cit., etc., may then be employed. These, however, entail giving other drugs as well which may be undesirable and is probably unnecessary so that the Ferri Carb., or Ferri Carb. Sacch. preparations are often preferred.

When the gastric disturbance is of a nature to demand an astringent the Ferri Perchlor. preparations are often useful. It is well to commence with only 5 minims but the official dose of 15 minims may often be exceeded later. In children in any case it is well to use a mild preparation and Syr. Ferri Phos. seems especially useful. As it often happens that the child is rickety the presence of phosphorus may possibly be of assistance—but this is not the place to discuss the use of phosphorus or its uselessness in rickets.

Adults often prefer the syrups to other preparations. The extensive use of iron pills is partly due to their convenience and partly perhaps to the fact that they do not blacken the teeth —a very potent bugbear to many patients. Of the pills which are official those who approximate in composition to the well-known Blaud's pill are the most generally useful. This contains 1 grain of Ferri Carb. in the 5-grain pill and is represented in the British Pharmacopœia by the Pil. Ferri and in the U. S. P. by the Pil. Ferri Carb. The dose is one to three pills but as a matter of fact, especially in chlorosis, it often seems advisable to give more. This entails rather a large bulk of pill and hence some physicians prefer to prescribe a smaller pill of the Ferri Carb. Sacch. or of Ferrum Redactum.

Certain drugs are conveniently prescribed with iron and various compounds are official in which two or more appear. It is not very easy to give arsenic with iron in the shape of a salt of iron because the amount of iron which can be administered without at the same time giving a poisonous dose of arsenic is necessarily small. Thus in the Ferri Arsenas the iron is too small in amount to have any appreciable effect. The Ferri Cacodylas is better in this respect and is to be preferred. It contains roughly 20 per cent. of iron and 60 per cent. of arsenic. It may also be used hypodermically (see below).

The Pil. Ferri Valerian. Co combines iron with the valerianates of quinine and zinc and has the advantage of enabling the physician to prescribe the necessary iron and the unpleasant but equally necessary valerian in a form which will not meet with the patient's disapproval.

The preparations of Ferri Iodidi have obvious uses but, qua iron, are not to be preferred to other preparations.

Ferri Peptonas, as already mentioned, does not blacken the teeth; it also has the distinction of being the only form of iron which seems to have been used for rectal administration; it is probably quite useless for the latter purpose as there is no evidence that iron is absorbed by the colon, but a good deal of evidence that it is excreted thereby.

The combinations of phosphorus with iron have already been mentioned and they do not in any way enhance the value of the iron so that, apart from their palatability, they only present whatever additional value may attach to the presence of phosphorus.

There are several preparations in which quinine and strychnine find a place as well as iron. These are similar to Easton's syrup and are more of the nature of tonics than of particular value in stimulating blood formation. The syrup and the elixir are equally palatable.

There are also marketed for internal use very many compounds which are alleged to contain iron in an especially assimilable form or else in a peculiarly non-irritating medium. Of these the most absurd are the preparations of hæmoglobin. Hæmoglobin is with difficulty digested and must in any case become something very different from hæmoglobin before it can be absorbed. Very much the same holds good of the majority of the patent "organic" preparations of iron but, at the same time, some of them do combine nourishment with medication and are useful to that extent. If, however, iron is not tolerated it is generally an indication to try a more suitable preparation of iron rather than to make use of some well-advertised proprietary medicine.

As to the dosage of iron no rule can be laid down—the various doses which are official in the subjoined list of preparations taken from the Codex with the omission of those which seemed unnecessary err rather on the side of being too small than otherwise.

It has become an established habit among many physicians to give large doses of iron in chlorosis—up to 20 grains three times a day. The writer is of the opinion that the results justify the practice nor need any intestinal disorder result. It is especially in chlorosis that the Mist. Ferri et Mag. Sulph. is useful.

In Addisonian anæmia iron is usually valueless but seldom, if ever, harmful. It therefore follows that it is often as well to give a small dose when the progress of the disease under arsenic alone is more than usually unsatisfactory. Of course only the mildest preparations should be given, *e.g.*, Ferri Carb. Sacch.

Although the practice of giving iron subcutaneously is a sufficiently old one it is only of comparatively recent years that it has become at all popular. This is perhaps partly due to the popularising of other methods of subcutaneous medication and partly due to the fact that it is only recently that needles suitable for its administration have become readily available.

In the subjoined list there are mentioned four preparations which have been or may be given—not, as a matter of fact, subcutaneously but intra-muscularly. Subcutaneous administration of iron is absolutely contra-indicated in all cases, it offers no advantages so long as asepsis is observed and it carries certain definite disadvantages, *i.e.*, local pain, induration and discolouration are to be expected to follow each injection. Other factors in the successful injection of iron are the needle and its cleansing. The needle should be of gold, platinum or iridium and should be washed in alcohol immediately after each injection, otherwise the needle can only be used once. A suitable spot for the injection is the buttock or, where it is not convenient for the patient to be in bed, the outer and back part of the upper arm.

The preparation most commonly used is the citrate or the Ferri et. Amm. Cit. Viridis. A 4 per cent. solution in distilled water should be prepared and 10 minims may be injected every second day. This is a relatively small dose. Some of the other preparations may be given in larger quantities, indeed so may the Ferri et Amm. Cit. Viride.

Lowenburg gives the following solution which seems rather a happy combination of iron and arsenic for intra-muscular administration, viz.

℞.	Ferri Citratis	0.018 gm.
	Sodii Cacodylatis	0.03 gm.
	Sodii Glycerophos	0.09 gm.
	Aq. Destillata	1.3 gm.

The indications for the intra-muscular administration of iron are few. In fact it is at present only used to any large extent for the purpose of discovering whether it has any advantages or for ministering to the mental insufficiency of those who desire some new thing, *i.e.*, with the intention to make use of the psychic as well as the therapeutic element. It is, however, an undoubted fact that drugs are as a rule more easily assimilated after hypodermic injection and this suggests that this mode of administering iron may be of value in cases of intense anæmia coming under observation only at a critical stage of the illness. It is also probable that the iron is not eliminated, *i.e.*, passed through the system, for many days after the administration. There is thus a constant supply of iron to the tissues for a relatively long period with only the trouble of a single injection as against the frequent giving of iron by the mouth.

Intravenous administration of iron may be expected to come into use for much the same reasons and as soon as it is realised that this is not a matter of introducing iron filings into the blood stream but merely of giving a mild and non-irritating iron salt or combination.

In conclusion the dangers of iron administration other than by the mouth must be mentioned. Iron, as one might expect from a near relative of arsenic, is very toxic—the symptoms being chiefly gastro-intestinal although very severe nervous symptoms have also been met with. This is an indication that the heroic doses of iron which may be given by the mouth must not be attempted by other methods of administration.

Preparation	Dose			
	By Mouth		Intramuscular	
	English	Metric	English	Metric
Ferri Arsenas	1/16–¼ gr.	4–16 mgm.	¾–1 ½ gr.	½–1 dg.
Ferri Cacodylas (daily)	¾–5 gr.	½–3 dgm.		
Ferri Carbonas Saccharatus	10–30 gr.	½–2 gm.		
Granulæ Ferri Carbonatis	30–60 gr.	2–4 gm.		
Massa Ferri Carbonatis	4 gr.	2½ dgm.		
Pilula Ferri (Blaud's)	5–15 gr	3–9 dgm.		
Pilulæ Ferri Carbonatis	5–15 gr.	3–9 dgm.		
Ferri Citras	5–10 gr.	3–6 dgm.		
Ferri Citro-arsenis Amm.	1/40–½ gr.	2–30 mgm.	½ gr.	30 mg. Twice a week
Ferri et Ammon Citras	5–10 gr.	3–6 dgm.		
Vinum Ferri	2 fl. dr.	8 mils		
Ferri et Amm. Cit. Viridis	5–10 gr.	3–6 dgm.	8–15 m. of 4 per cent.	½–1 mil. solution
Ferri et Amm. Tart.	5–10 gr.	3–6 dgm.		
Ferri et Quin. Cit.	5–10 gr.	3–6 dgm.		
Ferri et Strych. Cit	1–3 gr.	½–2 dgm.		
Ferri Glycerophosphas	1–5 gr.	½–3 dgm.	½ gr.	3 cgm.
Syr. Ferri Hypophos.	½–2 fl. dr.	2–8 mils		
Ferri Iodidum	1–5 gr	½–3 dgm.		
Pil. Ferri Iodidi	2 pills			
Syr. Ferri Iodidi	½–1 fl. dr.	2–4 mils		
Ferri Peptonas	5–10 gr.	3–6 dgm.		
Liq. Ferri Peptonatis	1–4 fl. dr.	4–15 mils		
Mist. Ferri et Mag. Sulph	½–1 fl. oz.	15–30 mils		
Liq. Ferri Perchloridi	5–15 m.	3–10 dmils		
Tinct. Ferri Perchloridi	5–15 m.	3–10 dmils		
Syr. Ferri Phosphatis	½–1 fl. dr.	2–4 mils		
Syr. Ferri Phos. c. Quin. et Strych.	½–1 fl. dr.	2–4 mils		
Elixir Ferri Quin. et Strych. Phos.	1 fl. dr.	4 mils		
Ferri Sulph. Exsiccatus	½–3 gr.	¼–2 dgms.		
Pil. Ferri Valerian. Co.	1–2 pills			
Ferrum Redactum	1–5 gr.	½–3 dgm.		
Ferrum Tartaratum	5–10 gr.	3–6 dgm.		

CHAPTER XXIII

THE BLOOD IN VARIOUS DISEASES

Actinomycosis.—There is usually a leucocytosis of from 12,000 to 30,000.

Acute Yellow Atrophy of the Liver.—There is a slight leucocytosis and frequently some degree of polycythæmia.

Addison's Disease.—This follows the general rules of tuberculosis but may have in addition a characteristic change, viz:—the occurrence of polycythæmia. The R.B.C. may be more than 7,000,000 per c.m.m. This, no doubt, depends on the stagnation produced by the extreme weakness of the heart but is not entirely dependent on this, for the bone marrow is sometimes to be found in a state of active hyperplasia.

Whether this is a purely compensatory hyperplasia or dependent on the tuberculous toxins has been questioned. The writer inclines to the former view but it is certainly of interest to remember in this connection the occasional association of polycythæmia with tuberculosis of the spleen.

Alcoholism.—In acute alcoholism a leucocytosis may be expected with the polymorphs in excess. This usually disappears in chronic alcoholism although the findings are not quite uniform.

In any doubtful case, however, the presence of leucocytosis is accounted for by the finding that the patient is suffering from alcoholic poisoning.

In chronic cases there is often anæmia.

Anæsthetics.—There is commonly a slight leucocytosis during and for a short time after chloroform and other anæsthesia. At the same time the activity of the individual white cell is diminished. The leucocytosis is at its height about twelve hours after the close of anæsthesia and then diminishes rapidly.

The red cells are always affected in some degree by anæsthesia and a diminished count—if not concealed by a concentration of the blood—is to be expected. In any case the hæmoglobin index is lessened and this is to be borne in mind when the question of operation on anæmic patients comes under consideration. Although some authorities say that no operation should be performed on a pateint who has less than 50 per cent. of hæmoglobin, the surgeon will no doubt—and quite rightly—lay more stress on the results of not operating than on the possible effects of an operation on the blood count.

Aneurysm.—Not very infrequently an aneurysm is mistaken for pus formation or, at least, the possibility of pus or a new growth is discussed. The blood changes help to the extent that there is no change if the aneurysm be not leaking and tend to cause confusion if it is since there is then probably leucocytosis.

The writer has a particular case in mind in which there was an abdominal tumour with anæmia and leucocytosis. A careful examination of the blood showed that there were a large number of red cells which were obviously of new formation, *i.e.*, were very polychromasic and rather larger than normal. There were also a few nucleated red cells. These two points were so strongly suggestive of hæmorrhage that the diagnosis of aneurysm was greatly strengthened as also the prognosis was rendered less favourable. The post mortem showed a very large abdominal aneurysm with very extensive leakage of blood into the surrounding tissues.

Ankylostomiasis.—There is commonly a very small degree of anæmia in those who are infected with the hook worm. In many people nothing worse seems to befall but in a few the anæmia may become very severe. There is no doubt that this worm is responsible for as much anæmia as any other single factor in many countries. It is, however, frequently found associated with other helminths. In Egypt there is considerable evidence to show that the Bilharzia is even more to blame for the prevalent anæmia, although the two commonly occur together. In China there is so great a variety of helminths to choose from that three or four species are quite commonly found in one individual and it is proportionately difficult to incriminate any one of them. Fluke infection is especially common. In other countries much the same conditions prevail to a less extent.

Miners' anæmia is always due to the ankylostoma since the conditions under which miners work, now largely improved in the more civilised countries, are favourable to the worm.

Eosinophilia is commonly met with but—as in other helminth infections—is not by any means invariable. It is probably a good sign in so far as it indicates a good reaction on the part of the patient and a bad sign in so far as it indicates, if extensive, a severe infection. This may seem a singularly inconclusive way of dealing with the matter but it is in accordance with facts so far as it is possible to ascertain them.

The writer has noted polycythæmia even during severe ankylostoma infection but in such case the hæmoglobin was nevertheless well below the normal.

Anthrax.—There are no marked blood changes but the bacillus may be isolated from the blood by culture or may even be visible in films.

Appendicitis.—Simple inflammation without the retention of pus or muco-pus in the lumen of the appendix does not lead to a leucocytosis. When the latter is present a diagnosis of pus formation is justified, but it gives no clue to the amount of pus. This must be decided by other means. A leucocytosis that is found to be increasing each day or is found to be over 20,000 when the case is first seen affords unequivocal indication for operative measures without delay. This holds good although the condition of the patient may appear exceptionally favourable. When an abscess has been drained the leucocytosis should disappear in the course of 36 hours at most. If it still persists there is still pus without free outlet or else general peritonitis is present. In the same way the occurrence of later complications such as sub-diaphragmatic abscess can be detected at the earliest possible opportunity. It is necessary to exclude other inflammatory complications such as pneumonia.

Arthritis (Chronic).—This does not usually give rise to any leucocytosis but may do so to a slight extent. The degree no doubt depends on the precise variety or stage of the process neither of which can at present be determined with any accuracy.

Asthma.—The eosinophil cells are increased and may reach high percentages such as 30 per cent. and 40 per cent. This is especially marked during the paroxysms and may persist for many months after the last one. The author has never failed to find more than the normal number of these cells in a genuine case. The presence of a septic process such as appendicitis soon abolishes the eosinophilia and in any case where there is a concurrent leucocytosis the percentage will be comparatively low—it is therefore the more important in this as in other diseases to have regard to the total number before laying emphasis on what may be very deceptive percentages. Unfortunately the total numbers are not often given when blood examinations are mentioned.

Baths.—A short cold bath causes slight leucocytosis—a long one produces leucopenia. A short hot bath causes leucopenia and a long hot one leucocytosis, *i.e.*, the opposite of what prevails in the former case. Neither the leucocytosis nor the leucopenia are extreme and they are probably local only, *i.e.*, there is no evidence that the white cell output of the marrow is increased and a local bath causes only local changes.

Massage acts as a long hot bath, *i.e.*, causes a leucocytosis.

Benign New Growths.—These as such have no influence on the blood although sundry cases have been reported in which some alteration of the blood co-existed with a benign new growth. In these cases no sufficient details have been given to connect the two. By interfering with internal secretions, pressing on glands, etc., this class of growth may have a variety of secondary results.

Beri-beri.—There is no characteristic change and no leucocytosis. Some authorities report an increase in the number of eosinophils.

Bilharziasis.—There is anaemia proportionate to the loss of blood that may have occurred from hæmaturia, etc., and commonly an eosinophilia. The latter seems to be more constant than in ankylostomiasis.

Blackwater Fever.—The blood condition is that which one would expect from the presence of loss of blood. Rarely there is a conditon approaching to that of Addisonian anæmia. If there is no intercurrent disease, such as chronic malaria or helminthiasis, the recovery from the anæmia is usually quick. Parasites have been detected in the blood by some observers, but their exact nature is not yet ascertained and the reports need confirmation.

Bothriocephaliasis.—It is a mistake to suppose as has been widely done that this is a disease in which the blood picture is that of Addisonian anæmia. It may be so in a few severe cases and undoubtedly is, but this is the case in almost every variety of anæmia that one can think of, and especially in those of a hæmolytic type.

Eosinophilia seems to be rather uncommon but is not by any means unknown.

Bronchitis.—Even the most severe cases do not show more than a very small rise in the number of leucocytes unless there is some pneumonia present.

Burns.—There is an immediate concentration of the blood and this gives rise to a symptomatic polycythæmia which may reach as much as 9,000,000. At the same time there is a rapidly increasing leucocytosis and this may reach as much as 50,000 in severe cases. The more marked these changes are the more likely is the case to prove fatal. The platelets are increased.

Caisson Disease.—There is a variable leucocytosis.

Cancer.—Small growths do not as a rule give rise to any change in the blood, unless they are so situated that they interfere with vital processes. Cancer of the stomach is peculiarly apt to produce a degree of anæmia quite out of proportion to any of the other signs of the disease. Indeed, other signs may be conspicuous by their absence when the anæmia is so profound that a diagnosis of "pernicious anæmia" is not infrequently made. The changes in the blood are sufficiently marked to make this mistake impossible if the blood is examined in a doubtful case. The hæmoglobin is disproportionately low in nearly every case and the larger nucleated red cells are seldom encountered. Moreover, there is very frequently a relative, if not an actual, leucocytosis: the polymorphs are usually of an immature type, viz., comparatively poor in chromatin, and not so much partite as is the case in most other anæmias particularly the Addisonian variety. These immature types of polymorphs are not so difficult to recognize as they are to describe. Their recognition is often of importance in cases that do not show an increase in the total number of leucocytes, but in which there are nevertheless reasons to suppose that the processes usually provocative of such an increase are at work. They then show that the bone marrow is really reacting to the best of its ability although the excitant is so toxic that it nearly paralyses the reactive power of the tissue. Such an increase of immature forms without a real leucocytosis may be seen in the severe types of streptococcal infections and in some cases of pneumonia. They connote a bad prognosis. If one loses sight of their presence and its significance there is danger that the nature of the disease may be similarly overlooked, because there is no "leucocytosis."

Cancer of Bone.—This includes osteo-sarcoma, myeloid sarcoma, multiple myeloma, etc. There is no change in the blood except the occurrence of leucocytosis in some cases. There is none in multiple myeloma or Kahler's disease.

Cancer with Metastases in Bones.—These cases may be associated with a somewhat peculiar condition of the blood. There is not ipso facto a great depreciation in the number of the red blood corpuscles, they may in fact be normal in quantity. The hæmoglobin is diminished to a varying extent. The unusual factor is the presence of nucleated red cells in considerable numbers, certainly in greater numbers than the degree of anæmia would lead one to expect. There may also be a considerable number of myelocytes found so that the picture approaches that of myelæmia. The total number of the white corpuscles is subject to great variation, the author has in three cases observed a diminution in the total numbers. These changes may be absent although there are undoubted metastases in bone, their importance lies in the confusion to which they are apt to give rise, viz., with Addisonian anæmia and with myelæmia. There is some evidence to support the view that they are due to a diffuse infiltration of the bone marrow with cancerous growth, and not to the stimulating effect of local deposits.

Considerable increase of eosinophil cells has been noted by some authors in association with malignant deposits in bone. This is rarely found.

Cerebral Tumors.—These are for some unexplained reason apt to be associated with anæmia greater than one would expect that the tumours themselves could be reasonably held responsible for. This may be a point of diagnostic importance, for in many cases the diagnosis rests on very few points and every one however insignificant, becomes worthy of note. The absence of anæmia is of no value as excluding tumour.

Cholera.—The diarrhœa causes concentration of the blood and the R.B.C. may reach 8,000,000 per c.m.m. There is an excess of leucocytes over and above that caused by the concentration and if above 20,000 this is said to be of bad prognostic import. The increase of the leucocytes lasts at least as late as the sixth day.

Chorea.—The eosinophils are increased in this disease and this is sometimes of importance when the exact nature of irregular movements is in question. While the eosinophilia persists the disease is not cured although the movements may have disappeared. It is to be remembered that children are provided with a larger number of eosinophils than are adults and small increases may be disregarded. An adult has normally not more than 250 per c.m.m. but a child may have 300 or 350 without being abnormal in this respect.

Cirrhosis of the Liver.—There is as a rule no change in the leucocytes dependent on the cirrhosis itself although there may be a leucocytosis depending on some associated condition. It is more frequently found in the hypertrophic cases. There is a varying degree of anæmia which appears to be due to the hepatic insufficiency in some way and to be more or less proportional to it. When jaundice is present there are other blood changes of particular interest to the surgeon (vide Jaundice).

Confusional Insanity.—Under this heading are grouped all the acute toxic and exhaustion psychoses, including puerperal insanity and generally the insanities "of times of life." There is always a leucocytosis at first and this may last for at least a year but in some cases it would seem to be variable, *i.e.*, not persistent even when the patient is not improving clinically. With convalescence it falls. This leucocytosis may reach as high as 40,000 but as a rule is between 20,000 and 30,000 and the polymorphs are in excess.

Some degree of anæmia, as judged of by hæmoglobin estimations, is usual but the red cells are seldom reduced but rather increased in number per c.m.m. This is probably a concentration and not a true increase.

Congenital Heart Disease.—According to the degree of functional disability induced by the malformation there is more or less polycythæmia. At first this is seldom more than 7 or 8 million per c.m.m. but later or in more severe lesions there may be more than 12 million red cells per c.m.m. There is no precise information available as to the progress from the smaller to the greater number but it would seem to proceed to some extent pari passu with the growth of the child. Adults with a disabling congenital heart lesion usually have a very high count and very seldom have less than 9 million.

On the other hand in severe cases the preliminary 7 or 8 million may rise very rapidly so that at the age of four or five years there are already as many as 12 million red cells per c.m.m.

The blood count seems to have little bearing on the prognosis in so far as mere numbers are concerned and more notice is to be taken of the degree of cyanosis—roughly, perhaps, an index of how far the increased count is adequate compensation for the lesion. If this is considerable and the count is high, *i.e.*, near the possible limit of about 13 million, then the prognosis is obviously bad for the child has little chance of developing any other means of compensation as might occur in the acquired heart disease of more adult life.

Quite a number of adults live to at least the third decade with a severe congenital heart lesion which is adequately compensated by a polycythæmia. These as a rule have little cyanosis except in cold weather, on exertion, etc. Still more reach the second decade and pass successfully through the various infective disorders of childhood.

In some cases of congenital heart disease—usually in premature children with severe lesions and no murmurs—there may be a very remarkable blood picture. Of this illustrations are given from a case investigated by the author (see Fig. 41). This blood picture may persist and the salient points may be accentuated as the child ages but the prognosis is very bad and the patient cannot be expected to live a year. It represents the persistence of an embryonic type of blood formation; whether in response to the extra demand for blood formation or as an "accidental" congenital deformity of the blood-forming tissues, these having failed to develop, cannot be said nor is it very material from a practical point of view. The author inclines to the latter view since many, in fact the majority, of severe cases do not show it in spite of a very great demand for compensatory blood formation.

In this type there are met with every possible sort of non-nucleated or nucleated red cell and the total number of nucleated red cells reaches very high—up to 60,000 in the writer's experience, possibly higher. The white cells are also increased and various myelocytes and pre-myelocytes are present in small numbers. Except for the absence of poikilocytosis the red cells are similar to those of Addisonian anæmia and the white to those of splenic anæmia of infancy but there is, of course, no anæmia but quite the opposite. Herein is the remarkable feature of the blood picture.

Convulsions.—In convulsions from whatever cause there is usually a rise in the number of leucocytes and this rise may reach as high as 30,000 to 40,000. Consequently a blood count should not be made until at least 12 hours after the last convulsion or the result may be quite misleading.

Cretinism.—There is no marked variation from the normal but there is a tendency for the hæmoglobin percentage to be unusually high. This is supposed to represent a reversion to the fœtal type of blood and disappears on the administration of thyroid extract.

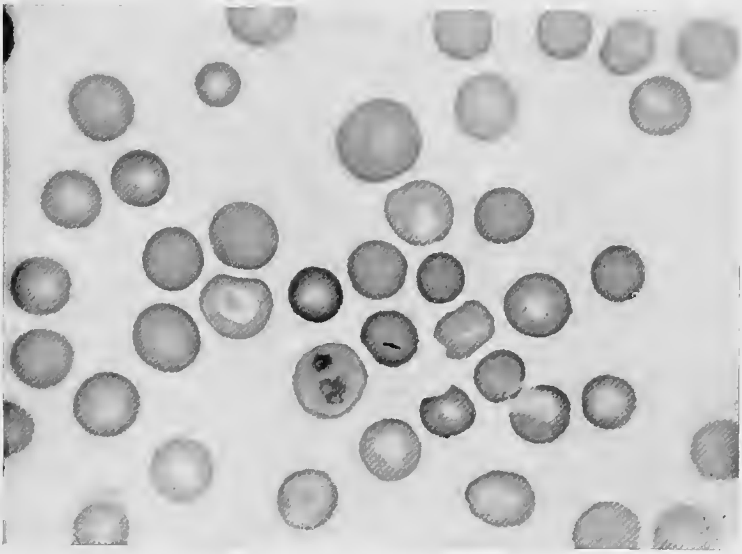


FIG. 41.—Microphotograph of the blood from a case of congenital heart disease in a premature child showing the variations in size and staining reaction of the red cells which are met with in embryonic life. A nucleated red cell having two nuclei is also shewn.

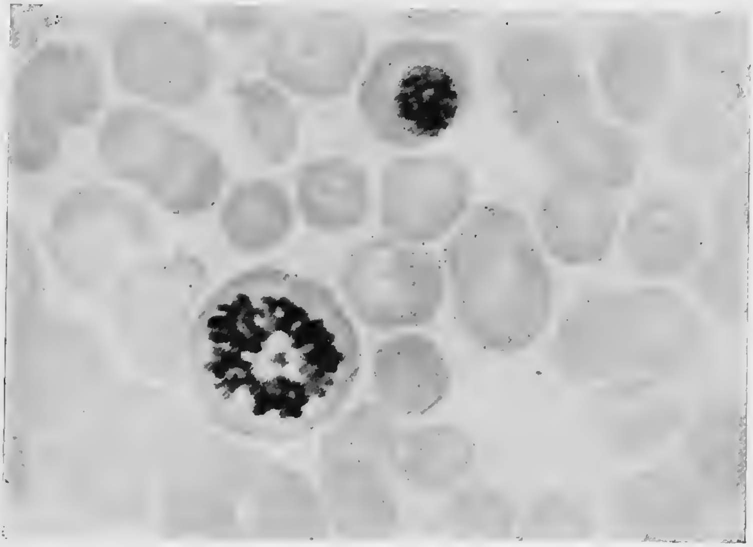


FIG. 42.—Another photograph from the same case shewing a mitotic figure in a megaloblast and a normoblast. These mitotic figures in nucleated red cells are commonly met with in myelæmia and the splenic anæmia of infants but are rarely discovered in other conditions.

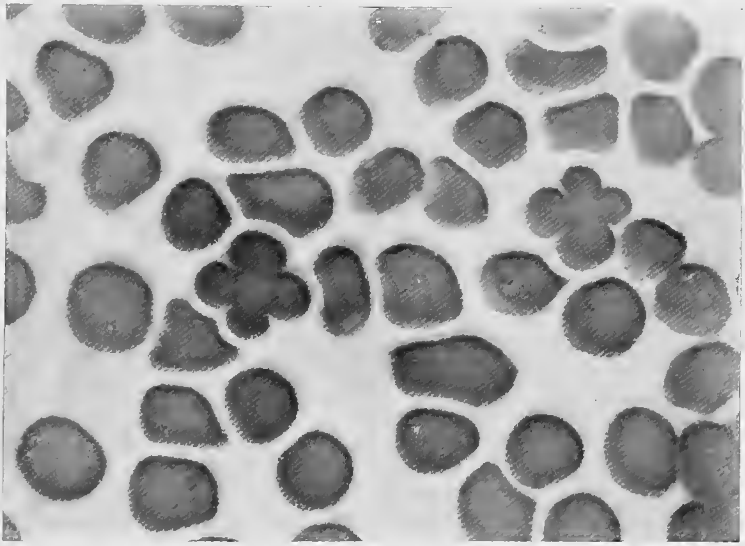


Fig. 43.—The blood from a case of congenital heart disease shewing variations in size of the red cells such as are common in premature children. The microphotograph also shews peculiar rosette forms which are artifacts and due to one cell lying over and constricting another. These forms are not very common but are not peculiar to any one condition.

Cystitis.—There is as a rule no leucocytosis although in very acute cases this may be present and the presence of kidney abscess will, of course, give rise to it.

Cystitis thus follows the general rule of abscess formation. *i.e.*, while the pus is not under tension there is no leucocytosis,

Dementia Præcox.—Here there is no leucocytosis and this may be a useful diagnostic point between this disease and the confusional insanities—in which, of course, the prognosis is very different. There is a tendency toward polycythæmia especially in those cases in which the disease is well established and the circulation is obviously suffering as shown by blue hands and feet, etc. This polycythæmia does not rise above 7,000,000 in most cases and the writer knows of no case in which it has reached 8,000,000.

Dermatitis Exfoliata.—There is a considerable increase in the eosinophils on the first day, in scarlet fever the eosinophilia comes later and is less pronounced.

Dermatitis Herpetiformis.—In this disease there is a great increase in the eosinophils and these cells may reach more than 40 per cent. The mononuclears are often increased at the same time.

Diabetes.—The blood of diabetics may be distinguished from that of normal persons by various more or less complicated reactions but these are not of interest to the practitioner since such examinations are not likely to be undertaken until diabetes has been diagnosed by some readier method.

There is no characteristic change in the red or white cells but the digestion leucocytosis may sometimes be unusually pronounced. Polycythæmia may be present.

Diarrhœa.—This tends to concentrate the blood and there is consequently a polycythæmia so far as the sample taken for examination is concerned although this does not naturally mean that the total number of red cells in the body is increased. This concentration is well marked in cholera and often in infantile diarrhœa.

Later if the diarrhœa continues anæmia begins to be apparent and may be very severe—below one million red cells per c.m.m. In prolonged diarrhœa anæmia is the rule.

Leucocytosis is variable according to the variety of the diarrhœa (vide Colitis, etc).

Digestion.—During digestion there is often a small increase in the leucocytes—one or two thousand above the average for the individual. The writer is not accustomed to make any particular allowance for this as a general rule owing to the uncertainty which prevails as to when this leucocytosis occurs. It is, however, well always to make a note as to the time at which a blood examination is made in order that subsequent examinations may be made at the same time, *i.e.*, presumably in the same relation as to time to the last meal.

This digestion leucocytosis affects both polymorphs and monomorphs. It is often absent in cancer of the stomach but is also so frequently absent in all sorts of diseases that its absence in cancer is almost useless as a diagnostic point. On the other hand if present and well marked it may be of some value as tending to exclude cancer.

Diphtheria.—Leucocytosis is the rule, reaching its height about the third day. The presence of myelocytes is not unusual. If present in large numbers they are of bad import.

Distomiasis.—This follows the rule which is commonly observed in parasitic diseases, *i.e.*, that an eosinophilia is usual but just inconstant enough to be annoying. It may, however, be said on this point that if a decided eosinophilia be present (over 10 per cent.) and there is no skin disease or asthma the probability of an intestinal or other parasite being present is very strong. The author has met with 60 per cent. of eosinophils in distomiasis. This was in an English case but in infection with the distomata of China, etc., so large an eosinophilia seems unusual.

There may be a considerable degree of anæmia—part of which at least in an individual case will be due to the distoma. It is marked by a considerable relative reduction of the hæmoglobin and closely resembles the anæmia of chlorosis.

Drug Poisoning.—Generally speaking there is a leucocytosis after any severe drug poisoning. Some substances produce also great destruction of the red cells and these have been mentioned as producing in consequence the hæmolytic type of anæmia, *i.e.*, a blood picture resembling that of Addisonian anæmia (see page 227).

Eczema.—In acute cases there may be an actual leucocytosis up to about 15,000. In many cases there is a relative increase in the eosinophils.

Emphysema.—In emphysema of the lungs there is usually some small degree of polycythæmia. In later cases this is more marked and is roughly proportionate to the amount of cyanosis. The hæmoglobin content of the red cells is usually somewhat lowered.

There is no leucocytosis due to emphysema but an eosinophilia is frequently noted in the literature. The writer has been unable to confirm these observations except in cases of emphysema complicating true bronchial, spasmodic asthma and in these there is no reason to suppose that the emphysema per se has any share in producing the eosinophilia.

Empyema.—Here there is a rising leucocyte count and much higher figures are reached than is the case in pleurisy. Any count above 15,000 should be considered strongly suggestive of empyema when there is any possibility of this occurring.

Endocarditis, Chronic, Non-malignant.—This is not accompanied by any leucocytosis except when, in early stages, it is associated with acute rheumatism. It does, however, give rise to changes in the number of red blood corpuscles. These are increased in all chronic cases when compensation is not adequate. Their increase is, however, not of much importance in these cases as there are many more important ways of judging of failure or otherwise of compensation. It is to be remembered, nevertheless, that such increases may occur for if they are met with when a cardiac lesion has not been suspected their presence may afford the first indication of heart disease.

Enteritis of Infancy, Acute.—In all conditions associated with acute diarrhœa in infants there is an increase in the leucocytes and this may reach more than 50,000. Anæmia is frequent but may be disguised by the concentration due to vomiting and loss of water from the bowel.

Epidemic Cerebro-spinal Meningitis.—There is a leucocytosis of varying degree. The opsonic index toward the meningococcus is markedly raised and is of diagnostic significance.

Epidemic Parotitis (Mumps).—There is no leucocytosis except at the beginning of the disease. It may then be about 12,000 to 13,000. The increase affects chiefly the mononuclears. If orchitis supervenes there is a larger leucocytosis and the polymorphs are in excess instead of the mononuclears.

Epilepsy.—For the condition of the blood during attacks see "Convulsions." Between attacks there is sometimes an increase in eosinophils but this is not large. The eosinophils are said to diminish during the three days preceding a fit and to increase after one.

Erysipelas.—Except in extremely severe cases there is an increase in the polymorphs and the leucocytosis may reach as high as in any case of pus formation. Leucocytosis is to some extent an index of the severity of the disease.

The writer is under the impression that the red cells as a rule suffer more severely in erysipelas than in most septic infections, *i.e.*, that there is more hæmolysis. Hence the red cells and the hæmoglobin content are diminished.

Erythema Nodosum.—There is not infrequently—possibly always—a leucocytosis in which the eosinophils are increased with the polymorphs. In septic processes the eosinophils are usually decreased when the polymorphs are increased.

Exercise.—After exercise, especially if prolonged or violent, there is a leucocytosis with relative increase of polymorphs and a tendency to absence of eosinophilis, *i.e.*, a leucocytosis of the infective type. It is of short duration and has vanished by the next day.

Exophthalmic Goitre.—The total number of leucocytes is diminished and there is often excess of lymphocytes. The latter very probably depends on an associated hypertrophy of the thymus and lymphoid tissues. The latter occurs in at least 50 per cent. of cases of exophthalmic goitre.

Fever.—Fever at first causes peripheral vaso-constriction and this with the loss of fluid due to perspiration leads to a concentration of the blood. A count will accordingly show an increase in the number of R.B.C. and also an increase in the total number of leucocytes. The relative proportions of each variety of leucocyte will not, however, be altered and if they are found to be, some other explanation than the fever per se must be sought.

When the fever subsides there is vaso-dilatation and the resulting fall in the numbers of R.B.C. is increased by an actual destruction of R.B.C. caused by the fever but previously masked by the concentration.

It will often be found that when fever is present the blood flows with unusual readiness from the puncture and that the R.B.C. are much more easily injured in the preparation of the film than is the rule.

Filariasis.—In cases of recent infection there is commonly a leucocytosis of about 20,000 per c.m.m. and the eosinophils may be increased up to 20 per cent. or more. In later cases there is less eosinophilia and less leucocytosis. Anæmia is variable but is not a striking feature in any case.

Follicular Tonsillitis.—There is usually a slight leucocytosis.

Fractures.—In a simple and uninfected fracture there is no change in the blood. With infection there may naturally be leucocytosis.

Frambœsia ("Yaws").—There is an increase of the lymphocytes.

Gall Bladder, Diseases of the.—Acute cholecystitis gives rise to the same rise in the leucocytes as accompanies the formation of pus elsewhere. If the inflammation subsides and the pus finds an exit the leucocytosis also subsides.

Gall-stone formation does not of itself give rise to any alteration in the blood but any accompanying inflammation of the gall bladder is apt to be associated with leucocytosis and the latter is roughly proportionate to the amount and intensity of the inflammation.

Cholangitis is similarly productive of leucocytosis.

When jaundice depends on obstruction to the bile passages, there is a delay in the time taken by the blood to coagulate and this is of considerable importance surgically.

Gastritis, Acute and Chronic.—In the former there is a leucocytosis and in the latter a leucopenia and nearly always a severe anæmia if the gastritis has led to atrophy of the mucous membrane.

General Paralysis of the Insane.—In early cases there is no increase in the W.B.C. In later stages it is a constant feature. The polymorphs are increased—often up to 80 per cent. or more. Convulsions in this as in other diseases produce a leucocytosis but the polymorphs are not then increased but the mononuclears. Eosinophilia is not uncommon. There is often some degree of polycythæmia, at least in cases that are not bed-ridden. This is probably physiological and due to the fact that the sufferer from this disease can count on being allowed to grow fat in comfort at the expense of his less fortunate brethren.

Glanders.—There is a moderate leucocytosis.

Gonorrhœa.—In acute urethritis there is a small increase in the number of leucocytes and the eosinophils are increased out of proportion to the other cells. The latter change occurs especially when posterior urethritis is present and may reach a percentage of 25 per cent.

Gout.—There is no characteristic change but there may be a leucocytosis during acute attacks.

If a drop of acetic acid be added to the serum obtained from the blood or a blister and a linen thread be left in contact with it uric-acid crystals will form on the latter. This test is not peculiar to gout but is obtained more readily in that than in any other disease.

Grain Itch.—There is slight leucocytosis and the eosinophils are increased to a moderate extent.

Herpes Zoster.—The largest increase in the leucocytes, not above 20,000, is found on the second day or on the third. The polymorphs and eosinophils are increased, the latter reaching a maximum during desquamation, they may reach 20 per cent.

Hydatid (Echinococcus).—So long as an hydatid cyst is alive and active there is an eosinophilia in the circulating blood. It may be small or merely a relative without an absolute increase but it is almost unknown that it should be absent.

If suppuration takes place in the cyst or it becomes dead and calcified or necrosed, the eosinophilia disappears.

Anæmia is not a factor in hydatid disease.

Hysteria.—The blood is normal unless there be some other cause for abnormality. This negative finding is often of importance in diagnosis of obscure cases but it is as well to be absolutely sure as far as man may be by seeing that the iodophil reaction is not present. The author has in mind two cases in which severe pain was complained of and in which the diagnosis of hysteria was possible in one and had been made in the other. The latter had suffered many years from this diagnosis and had become a morphia habitue eight years before his blood was examined. Both shewed well-marked iodophilia, with an otherwise normal blood count. The first had a cerebral tumour and died therefrom. The second had very chronic pancreatitis and duodenitis. He was operated upon, lost all his pain, gave up morphia and went back to work after eight years' absence. But he had suffered for eight years because there was no evidence come to light on which a surgeon would operate.

Influenza.—There is no leucocytosis but rather a leucopenia. The presence of leucocytosis means the presence of complications such as pneumonia or meningitis.

Insanity.—See under Confusional Insanity, Dementia, etc.

Intestinal Obstruction.—Leucocytosis may reach 20,000 in a few hours, it falls to normal in most cases in about five days. An early fall suggests the onset of gangrene or fatal auto-intoxication. The manner or site of the obstruction make no difference. Chronic partial obstructions do not follow these rules. They remain true of intussusception.

Jaundice.—In all cases of jaundice (except the acholuric form) there is a delayed coagulation time of the blood. The red blood cells are often larger than normal and their resistance to hæmolysis by salt solutions is increased. On the other hand their resistance to hæmolysis by saponin and other blood-destroying agents is diminished.

Lead Poisoning.—In lead poisoning the anæmia is a very early symptom—usually if not always antedating any sign of paralysis. This anæmia is marked by the extreme frequency of cells showing all sorts of stippling or basophil granulation. In severe cases there may be all the hæmatological signs of

Addisonian anæmia—another proof of the fallacy of regarding the blood picture as a criterion of this disease from which there is no appeal.

The basophilia is so marked that it is possible by routine examination to exclude among those who are engaged in lead industries those who are about to suffer from the disease before other signs appear. Such routine examination has not been done, so far as the author is aware in other countries, but is in force in Germany.

Leprosy.—The blood is normal in anæsthetic cases but in the nodular form there may be an increase in the eosinophils. The lepra bacillus has been found in the blood on several occasions. In old cases and in old people there may be a considerable degree of anæmia.

Lupus.—There may be an increase of the eosinophils.

Malaria.—As already stated no attempt will be made to describe the malarial parasites. The red cells fall very considerably in severe cases and the blood picture of Addisonian anæmia may be reproduced. In other cases there is a secondary anæmia with low hæmoglobin index and in even others there may be an aplastic anæmia so severe that there is practically no reaction on the part of the marrow.

The fall in red cells, as would be expected, is most marked after a paroxysm and may be very rapid so that a week or two of fever is sufficient to lower the number of red cells by more than half the total amount. All sorts of qualitative changes are present, poikilocytosis, polychromasia and presence of large pale cells deficient in hæmoglobin.

The condition of the red cells is, however—except when the parasite is present—in no way diagnostic of malaria.

The changes in the white cells are more important. There may be a slight leucocytosis during the paroxysm but this is of short duration and gives place to leucopenia, which latter not infrequently falls below 2000 per c.m.m. The lymphocytes remain at about the normal number but the polymorphs and eosinophils are diminished. The only cell which is increased is the transitional leucocyte or large hyaline cell. These may reach as high as 30 per cent. of all white cells present. They often contain pigment granules even when there are no malarial parasites to be found in the circulating blood. In a few cases there has been a marked leucocytosis in malaria, either terminal, *i.e.*, when the patient was moribund or, apparently, in negroes who possessed some degree of natural immunity to the disease and recovered without the use of quinine.

Malignant Endocarditis.—This is always associated with a rise in the number of leucocytes and a figure of about 25,000 is quite frequent. It is, however, dangerous to give figures in this or any other condition as the extent of the rise naturally depends on the patient's resistance and this will be found a very variable factor. All numbers quoted are therefore to be understood as those of most usual occurrence.

Malta Fever.—There is a normal leucocyte count or a leucopenia with relative increase of the mononuclears.

The serum "clumps" the micrococcus melitensis and the speed of development and the degree of clumping are to some extent indicative of the probable course of the case. Good clumping means a good prognosis.

Mania, Acute Delirious.—There is a high leucocytosis but the state of the patient is not such as to render a blood examination a very easy procedure nor does it assist in the diagnosis to any marked extent. In a case suspected of malingering, it might be of use but it is very difficult to simulate acute delirious mania for long.

Measles.—There is a leucocytosis in the pre-eruptive stage but W.B.C. fall to normal as the rash comes out. They may rise again later but this is due to inflammatory complications and should direct attention to their occurrence if they are not obvious clinically.

German measles or Rotheln has a similar blood condition but the changes are apt to be less marked.

Melancholia.—There is often a leucocytosis, especially at first, and later the tendency to polycythæmia which is so usual among the insane shows itself. Nevertheless the hæmoglobin is commonly reduced.

Moribund States.—Before death there is sometimes a very remarkable leucocytosis in which either the polymorphs or lymphocytes may be in excess, usually the latter. The blood picture may become very similar to that of leukæmia. This leucocytosis occurs from one to two days before death. It is not met with in all cases nor in sudden death. The author has not met with a typical case and so is unable to say whether there are any abnormal cells, *e.g.*, cells of the white series showing mitosis or embryonic cells—presumably there are not. A similar terminal rise is not infrequently met with in leukæmia even when the white cells have been at a high figure for some time previously.

Morphinomania.—This is one of those diseases in which a false pallor is commonly present so that the patient appears always anæmic in spite of the fact that his blood count may be above normal.

A leucopenia is fairly common but otherwise the blood shews no change.

Mycosis Fungoides.—In this as in all the cases which are classed with this disease or under such titles as lymphodermia perniciosa or multiple sarcoma of the skin, the blood findings as reported have been very variable. In many cases the blood picture of leukæmia has been noted and these ought to be reported as cases of leukæmia with skin lesions rather than as examples of mycosis fungoides. In other cases, apparently similar clinically, there has been a normal count or a leucocytosis. Where a leucocytosis is reported, with the polymorphs in excess, and there is no infection of the skin lesions sufficient to account for it, the probability of sarcoma is increased. Cases with a normal count can be relegated to the mycosis fungoides group until proved to belong to some other but a blood examination should always be made. There are no clinical features which serve to distinguish leukæmia or sarcoma from mycosis in any individual case and the histological features usually admit of question.

All these diseases tend to terminate in severe anæmia, another sign that they are near akin, and this is apparently of the secondary type with reduction of hæmoglobin in excess of that in corpuscles and with leucopenia—but it is difficult to be sure enough of the diagnosis to make definite statements about this point.

Myelitis, Acute (of the Spinal Cord).—This may produce a marked and persistent leucocytosis.

Myocarditis.—The chronic form gives rise to an increase of red corpuscles as does valvular disease; here also the practical importance of recognising the change will not often be apparent. In the acute myocarditis of various fevers and intoxications the importance of recognising polycythæmia is much more apparent. When the degree of concentration of the blood seems to be greater than can be explained by the loss of fluid by perspiration, etc., that is when the count approaches 7,000,000, the possibility of myocardial degeneration is at once to be suspected. In several cases the author has been able to direct attention to cardiac lesions before unsuspected by an examination of the blood—the latter as a rule undertaken in the first place with the hope that it might throw some light on the nature of the fever. These blood changes are more fully dealt with under the heading of Symptomatic Polycythæmia.

Myxœdema.—There is no characteristic change in the blood, but some authorities report the finding of myelocytes without other apparent cause.

Nephritis, Acute.—Nearly always there is a marked degree of anæmia and this no doubt plays its part in the production of the typical facies but the latter is also due to the large amount of water in the tissues. The facies of many cases of chlorosis is not dissimilar and owns a parallel explanation. Leucocytosis is to be expected and is apt to persist for a long time especially in the presence of uræmic symptoms or in post-scarlatinal cases.

Nephritis, Chronic.—Anæmia is very variable and there may be polycythæmia.

Neuritis.—In lead neuritis there is no leucocytosis but in alcohol neuritis there may be an increase up to as much as 20,000. The same is true for neuritis associated with fever and presumably due to some infective agent. In beri-beri there is no leucocytosis.

Obesity.—Most people who suffer from this perversion of metabolism have an actual plethora and the number of R.B.C. is increased above the normal. In the minority there may be some degree of anæmia.

Osteomalacia.—There is no characteristic change in the blood. There may be some anæmia but the same is true of all other diseases with very few exceptions.

Pancreatitis.—In acute pancreatitis there is a moderate leucocytosis, in chronic cases there is none and even may be a leucopenia. Iodophilia may be present even in the latter cases and suggest the presence of inflammation. In chronic cases there may be a degree of anæmia simulating Addisonian anæmia.

Parasites, Intestinal.—Other than those which have been dealt with under Ankylostomiasis, etc., there are a great number of intestinal parasites encountered in man and the number is increasing with the increase of the facilities for research. Eosinophilia is very common but is not the rule, *i.e.*, not a finding on which one may rely for the exclusion of intestinal helminthiasis. It may reach very high figures, well over 50 per cent. of all white cells, but more commonly is only a slight increase to 7 or 8 per cent. or even only a relative increase.

Pemphigus.—This leads to an increase of the eosinophils, it is thus distinguished from variola, etc. In the form known as epidermolysis bullosa eosinophilia is very slight or absent. The bullæ of streptococcal dermatitis are associated with an absence or diminution of eosinophils.

Pericarditis.—This cannot be distinguished from any other inflammatory condition by the blood count; it follows the general rule that a rising count means pus formation and that tuberculous processes do not, as a rule, lead to any rise in the count.

Peritonitis.—In tuberculous peritonitis there is no leucocytosis but in all other forms associated with the invasion of pyogenic organisms it is present and usually to a considerable extent. It would be absent if no reaction were taking place but this is extremely uncommon.

Pertussis (Whooping Cough).—There is a relative and actual increase in the mononuclears and an actual increase of the polymorphs to a less extent. There is a case on record in which the leucocytes reached the very high figure of 236,000 per c.m.m. Higher counts than 100,000 are very rare in any other disease except in those in which the overproduction of leucocytes is the predominant feature, *e.g.*, myelæmia and lymphæmia. In whooping cough the increase of the white cells precedes the development of the characteristic cough.

Phlebotomus or Sand-fly Fever.—Leucopenia is an almost constant sign and this is of considerable diagnostic value. Counts of less than 3000 W.B.C. are often met with, the polymorphs are relatively diminished.

Phosphorus Poisoning.—There is often a polycythæmia for a few, two or three, days and a leucocytosis. The latter, however, is fugitive and may not last so long as the polycythæmia.

Plague (Bubonic).—There is a moderate leucocytosis and sometimes some degree of polycythæmia. Aoyoma reported a very large leucocytosis in some cases but this was not confirmed by the Austrian plague commission.

Pleurisy.—In tuberculous pleurisy there is no leucocytosis, in simple inflammatory pleurisy there may be up to 15,000 white cells per c.m.m. but even this is not usual. This is important from a diagnostic point of view since a persistent or a high leucocytosis indicates empyema.

Pneumonia, Lobar.—There is a leucocytosis of about 20,000 in a case of average intensity. In a case that is clinically severe the absence of leucocytosis is of fatal significance, in a less severe case it may be due to the mildness of the infection and not, as in the severe case, to the absence of reaction. The re-appearance of eosinophil cells, which are absent from the circulating blood during the height of the fever, is of good prognostic import, so also is a fall in the relative numbers of polymorphs.

Poisoning by Aniline Dyes.—This is not very uncommon and may be met with in a chronic form amongst those who are exposed to the fumes of these dyes during their manufacture, in those who have acquired a habit of taking them, and in miners who may be exposed to the fumes of allied substances after the slow combustion, as against explosion, of a charge. Cases of suicide also occur and cases of accidental exposure.

The outstanding symptom is cyanosis and the blood on examination gives the spectroscopic bands of methæmoglobin, and shows different changes according to the stage at which the case is seen. In the first stage there are to be seen fragmented red cells and cells deficient in hæmoglobin but no poikilocytes or megalocytes and no nucleated red cells. Later there is a very marked leucocytosis and, similarly, a reaction on the part of the red cells so that there are now many nucleated red cells and all forms of "degenerate" cells. Later still, if the patient survives, the blood slowly returns to normal.

Psoriasis.—There is an increase of the eosinophils.

Puberty.—In the woman there is a fall in hæmoglobin and in the specific gravity of the blood as a whole at the time of puberty, although the plasma does not suffer but is if anything richer than normal. The changes are, in fact, those of chlorosis on a smaller scale.

It is probable that a less but similar change takes place in the male but this has been little investigated.

Pyæmia.—This is one of the disorders in which when acute a high leucocytosis is the rule—up to 70,000 or 80,000 in some cases and often over 50,000. Anæmia is invariable although it may be masked by concentration due to excessive sweating, heart failure, diarrhœa, etc. The hæmoglobin falls rapidly in acute cases and does not recover for a long while even if it prove possible to arrest the septic process.

Rabies (Hydrophobia).—The absence of at least a relative increase in the polymorphs would be very much against a diagnosis of rabies. In most cases the total count is increased. If the case has been treated the blood will be found to be normal.

Relapsing Fever.—There is leucocytosis and this is most marked just after the crisis. The spirilla are to be found in the blood during the fever and when the fever has subsided the serum has the power of immobilising spirilla. This may be tested by mixing equal parts of the patient's serum and blood from a case which shows the spirilla. If the bactericidal power lasts as late as the seventh day in sufficient strength to immobilise spirilla in less than one hour there will be no further relapse.

Rheumatism, Acute.—This is accompanied by a very marked rise in the leucocyte count, reaching 25,000–30,000 in an average case. There is also a considerable increase in fibrin formation which may be detected by allowing a small drop of blood to remain under a clean coverslip ringed round with vaseline for some minutes. Under the oil immersion lens it is then quite easy to see the strands of fibrin and a little experience will soon make it possible to say whether it is increased in amount or not. In normal blood the fibrin strands are not very obvious and even when fully deposited do not form a very thick network. This increase in fibrin is also seen in pneumonia.

Rickets.—It is common knowledge that rickets is often associated with some degree of anæmia. This is asserted as an accurate clinical generalization. It may be so but it is not an accurate pathological one. Rickets per se does not cause anæmia, the latter when present is due to the associated malnutrition or other adverse circumstances. It is important to remember that the treatment of this anæmia should be actively directed to its cause. It is not adequately dealt with by any convenient iron preparation.

It is also to be remembered that children have relatively less hæmoglobin than adults and more leucocytes, otherwise trouble may arise in the interpretation of blood counts in this and other conditions, which are peculiar to children.

The disease discussed under the title "Splenic Anæmia of Infants" is very often associated with rickets.

Scarlet Fever.—Leucocytosis is present about 24 hours before the rash appears and usually terminates about the same time as the fever. It reaches 18,000 to 30,000, and 40,000 is not an infrequent figure. The eosinophils increase from about the fourth day onward and their absence is a bad prognostic sign. It will be noted that the blood condition affords a means of diagnosing as between scarlet fever and measles.

Scleroderma.—There is an eosinophilia.

Scurvy.—There are no characteristic blood changes but a secondary anæmia proportionate to the hæmorrhage and general malnutrition.

Splenectomy.—After splenectomy there is commonly an immediate and considerable rise in the number of leucocytes—up to 30,000 to 40,000 or more. This may develop after a few days but more usually is found on the day after operation and falls during the ensuing one or two days to a little above normal. After this time the number of leucocytes varies but there is often a slight leucocytosis for many weeks, months or years.

In this the lymphocytes are in excess and also the eosinophils and the two changes are progressive for an indefinite period, *i.e.*, they have been found still present and increasing four or five years after operation but the increase is very slow.

In some cases these changes are not present and we do not know sufficient to be able to offer any explanation of why this should be. As is well known there is not infrequently hyperplasia of the superficial lymph glands after splenectomy and this would appear to offer a reason for the lymphocytosis. On the other hand the lymphadenoma may be absent and yet the lymphocytosis present. This, for the sake of argument, may be explained as due to hyperplasia of internal lymph glands and it is a fact that there is usually hyperplasia of this nature. In any case the hæmolymph glands which lie in the retroperitoneal tissue at the side of the aorta are enlarged since they take on the functions of the spleen—fortunately they do not seem to take on its disorders too, so that splenectomy for, *e.g.*, splenic anæmia, does not lead to anæmia due to hypertrophy of the hæmolymph glands but to a cure of the condition.

Starvation.—This causes an increase of the numbers of red blood corpuscles and this is proportionate to the amount of water or fluid taken. The W.B.C. are, of course, affected by the concentration and vary within narrow limits. If the fast has been long prolonged there is an actual hyperplasia of the bone marrow as would be expected. Polycythæmia in hospital patients is far more often caused by starvation than is recognised. It is found not only in the case of those who are unable to obtain food but in those who are not able to assimilate it.

Sunstroke and Heat Exhaustion.—Nearly all cases show some increase in the number of W.B.C. at some time but the time and the extent of the rise seem to vary according to ill-understood circumstances.

Synovitis.—This, unless rheumatic, is accompanied with only a slight leucocytosis—not more than 15,000 or 20,000 at the most. The presence of pus in a joint may of course give rise to a higher count.

Syphilis.—The spirocheta pallida has a direct destructive influence on the R.B.C. and there is consequently anæmia; this may become very extreme but why it is mild in some cases and severe in others is a matter for speculation.

In the secondary stages, especially when there is a roseola present the W.B.C. are usually increased and myelocytes may appear. There is an increase of eosinophils when the rash is a prominent feature.

In the later stages there may be a leucopenia and in all stages a relative lymphocytosis is common. General paralysis seems to be an exception to this rule for there is usually a leucocytosis with relative increase of the polymorphs and the latter is present even when the total numbers are not higher than normal.

Treatment should be directed rather to the syphilis than to the anæmia but the addition of iron seems to have a good effect. It, however, improves the condition very slowly. It is well to remember that many people who have tertiary syphilitic lesions have blood changes due to quite other causes.

Tetanus.—There is a moderate leucocytosis and the eosinophils are not diminished as is the rule in toxic leucocytosis.

Thoracic Duct.—Rarely the thoracic duct is affected by some septic process and becomes converted into an abscess cavity. This may then drain directly into the veins at the root of the neck and a huge leucocytosis results. This may reach over one hundred thousand white cells per c.m.m., a condition of affairs hardly ever met with in any other septic condition.

Trichiniasis.—This is one of the diseases in which there is commonly a very considerable degree of eosinophilia, *i.e.*, up to 60 per cent. or more. The other blood changes are few or none.

Trypanosomiasis.—Other than the presence of parasites there are no changes but secondary anæmia.

Tuberculosis.—There is not as a rule any leucocytosis in tuberculosis, except in the pneumonic form. It is sometimes present in meningitis especially in late cases but is absent in acute miliary tuberculosis. The presence of leucocytosis therefore indicates in the majority of cases some complication. Of all complications the secondary septic infection of cavities in the lungs is the most common. In all forms a relative lymphocytosis is the rule and a high proportion of monomorphs is not a favorable sign unless the disease is obviously quiescent and the blood formula returning to normal.

Anæmia is an early symptom of tuberculosis but is often more apparent than real. If in a young person there is obvious pallor but the number of R.B.C. is not below normal, although the hæmoglobin is, there is a great probability that the disease is either chlorosis or tuberculosis. The differential diagnosis does not entail any particular difficulty.

The same caution is necessary as in the case of syphilis, namely that many people with tuberculous lesions have some degree of anæmia or other blood change that is in no way dependent on the tuberculosis.

Typhoid Fever.—Leucopenia is always present and is apt to be proportional to the severity of the case. It is a valuable point in differential diagnosis especially from appendicitis. The presence of a leucocytosis means the presence of complications. The appearance of leucopenia precedes the development of a positive Widal reaction.

Typhus Fever.—The leucocyte changes are in dispute but it seems probable that in most cases there is a definite increase. This reaches a maximum shortly before the crisis and falls during convalescence. The complete absence of eosinophils is not a good sign.

Variola (Small Pox).—Before suppuration sets in there is an increase of mononuclear cells, among these myelocytes are often met with. Later there is a polymorphonuclear leucocytosis.

Varicella (Chicken Pox).—The blood changes are similar to those of variola but less in degree.

Vaccination.—This leads to a leucocytosis increasing as the pustules mature.

Vaccinia.—The blood is normal in generalised vaccinia.

Xeroderma Pigmentosum.—There may be a large leucocytosis and in many cases there is a moderate increase of the eosinophils.

Yellow Fever.—This is one of the diseases in which leucocytosis is usually absent. There is no relative increase of lymphocytes as is commonly seen when leucocytosis is absent in an acute febrile infection. This is in contrast to the increase of mononuclear cells in malaria. The plasma is often found to contain free hæmoglobin and there may be a considerable degree of anæmia, often with the presence of nucleated red cells.

INDEX

Acholuric jaundice, 221
Actinomycosis, 356
Acute aplastic anæmia, 186
        blood, 187
        course, 187
        marrow, 187
        pathology, 186
    gastritis, 369
    myelitis, 375
    rheumatism, 379
    yellow atrophy of liver, 356
Addisonian anæmia, 235
      age, 238
      alimentary system, 247
      allied diseases, 237
      asepsis, 257
      auditory system, 241
      blood, 243
      circulatory system, 241
      clinical varieties, 251
      combined sclerosis, 239
      complications, 251
      course, 250
      definition, 235
      diagnosis, 252
      diet, 258
      duration, 251
      etiology, 238
      fever, 240
      general pathology, 235
      general symptomatology, 239
      glossitis, 247
      liver, 248
      marrow, 242
      metabolism, 250
      nature, 235
      nervous system, 239
      olfactory organs, 240
      onset, 239
      ophthalmic system, 241
      oral sepsis, 252
Addisonian anæmia, pigmentation, 245
      relapses, 251
      remissions, 250
      respiratory system, 247
      sepsis in, 252
      sex, 238
      skin, 246
      sore tongue, 247
      spleen, 242
      synonyms, 235
      urine, 248
Addison's disease, 356
Adenie, 110
Administration of arsenic, 347
      iron, 349
Adrenal disease, 356
Adrenal sarcoma, 69
Alhumosuria, Bence-Jones, 134
    myelopathic, 134
    in lymphæmia, 76
    tests for, 135
Alcoholism, 356
Altitudes, effect of, 176
Anæmia, acute aplastic, 186
    Addisonian, 235
    aplastic, 186
    atrophic, 191
    congenital, 188
    false, 197
    miners', 357
    myelophthisic, 191
    pernicious, 235
    phagocytic, 276
    secondary, 191
    senile, 220
    septic, 191
    splenic, of adults, 137
    splenic, of infants, 214
    symptomatic, 191
    tropho-neurotic, 191
Anæmic vomiting, 209

Anæsthesia in lymphatism, 153
Anæsthetics, 356
Aneurysm, 357
Aniline dye poisoning, 377
Anisocytosis: *abnormal variation in size of the red cells but not necessarily in shape*, 227
Ankylostomiasis, 357
Anthrax, 358
Aplastic anæmia, 186
Appendicitis, 358
Arsenic, administration of, 347
  poisoning, 348
Arthritis, 358
  in hæmophilia, 326
Ascites, chylous, 100, 102
  in myelæmia, 101
Associated syndromes of leukæmia, 82
Asthma, 359
  thymic, 150
Atrophic anæmia, 191
Autoerythrophagocytosis, 276

Banti's disease, 137
Basophil granulation vide stippling, 244
  leucocyte vide mast cell, 36
Basophilia: *a term used to include stippling and polychromasia*
Baths, 359
Bence-Jones albumosuria, 134
    in lymphæmia, 76
Benign new growth, 359
Benzol therapy, 108
Beri-beri, 359
Biermer-Ehrlich anæmia, 235
Bilharziasis, 359
Blackwater fever, 360
Blindness in anæmia, 197
Blood cells, origin of, 50
  composition of, 31
  crisis, 183
  diseases, classification of, 17
    definition of, 17
    table of, 24
  dust, 39
  examination, 40
  -forming organs, 26
Blood platelets, 38
Bothriocephaliasis, 360
Bronchitis, 360
Bronzed diabetes, 262
Burns, 360

Caisson disease, 360
Cancer, 360
  and myelæmia, 90
  of bone, 361
  with bone metastases, 361
Carbon monoxide poisoning, 283
Carboxyhæmoglobin, spectrum of, 284
Carboxyhæmoglobinæmia, 283
  blood in, 289
  definition, 283
  diagnosis, 290
  general pathology, 284
  general symptomatology, 286
  nature, 283
  synonyms, 283
  treatment, 291
Cerebral tumour, 362
Cerebro-spinal meningitis, 367
Chicken leukæmia, 50
  -pox, 382
Chloroma, 88
Chlorosis, 306
  age, 306
  alimentary system, 309
  blood, 314
  circulatory system, 308
  complications, 316
  course, 316
  definition, 306
  diagnosis, 317
  Egyptian, 191
  general symptomatology, 307
  nature, 306
  nervous system, 311
  onset, 307
  predisposition, 307
  respiratory system, 309
  sex, 307
  skin, 313
  spleen, 314
  termination, 316
  thrombosis, 309

Chlorosis, treatment, 318
  tuberculous, 191
  urogenital system, 310
  urine, 311
Cholæmia, 221
  age, 225
  alimentary system, 229
  allied diseases, 224
  blood, 227
  circulatory system, 226
  clinical varieties, 232
  complications, 232
  course, 231
  definition, 221
  diagnosis, 232
  duration, 232
  etiology, 224
  fever, 226
  gall stones, 230
  general pathology, 221
  general symptomatology, 226
  liver, 230
  lymphatic system, 229
  marrow, 226
  nature, 221
  nervous system, 226
  onset, 225
  osseous system, 229
  respiratory system, 229
  sex, 225
  skin, 231
  spleen, 228
  splenectomy, 234
  synonyms, 221
  treatment, 233
Cholecystitis, 369
Cholera, 362
Cholesterin therapy, 233
Chorea, 362
Chronic cyanotic polycythæmia, 155
Chylous effusion in myelæmia, 100
Cirrhosis of liver, 362
    in hæmochromatosis, 262
    in splenic anæmia, 143
Classification of blood diseases, 17
Clubbing, 180
Coagulation time, estimation of, 47
Coal gas poisoning, 283
Coley's fluid, 105
Combined sclerosis in Addisonian anæmia, 240
    in myelæmia, 93
Confusional insanity, 362
Congenital acholuric jaundice, 221
  anæmia, 188
  heart disease, 177, 363
  myelæmia, 92
Convulsions, 364
Count, differential, 44
Cretinism, 364
Cryptogenetic polycythæmia, 155
Cyanosis, 279
  causes of, 279
  enterogenous, 292, 298
  idiopathic, 292
  microbic, 298
Cystitis, 365

Dementia præcox, 365
Dermatitis herpetiformis, 365
  exfoliata, 365
Dermographia in erythræmia, 168
Diabetes, 365
  bronzed, 262
Diarrhœa, 365
Differential count, 44
Digestion, 366
Diluting fluids, 40
Diphtheria, 366
Distomiasis, 366
Drug poisoning, 366

Echinococcus, 370
Eczema, 367
Egyptian chlorosis, 191
Emphysema, 367
Empyema, 367
Endocarditis, 367
  malignant, 373
Enteritis, 367
Enterogenous cyanosis, 292, 298
Enumeration of blood cells, 42
Eosinophil leucocyte, 35
  leucocytosis, 303
Eosinophilia, 303
Epidemic cerebro-spinal meningitis, 367
  parotitis, 368
Epilepsy, 368

Epithelioma of spleen, 130
Epitheliome primitive, 130
Erysipelas, 368
Erythema nodsum, 368
Erythræmia, 155
  age, 158
  alimentary system, 166
  allied diseases, 157
  blood, 163
  circulatory system, 161
  clinical varieties, 169
  complications, 170
  course, 169
  cyanosis, 168
  definition, 155
  dermographia, 168
  diagnosis, 170
  duration, 169
  erythromelalgia, 162
  etiology, 157
  general pathology, 156
  general symptomatology, 158
  liver, 167
  marrow, 162
  mucous membranes, 168
  nature, 155
  nervous system, 159
  onset, 158
  osseous system, 166
  respiratory system, 166
  sex, 158
  skin, 168
  special senses, 160
  spleen, 165
  splenectomy, 172
  synonyms, 155
  thrombosis, 162
  treatment, 171
  urogenital system, 167
Erythroblasts: *nucleated red cells*, 33
Erythrocytes: *red cells*, 32
Erythromelalgia, 162
Examination of blood, 40
Exercise, 368
Exophthalmic goitre, 368
Experimental leukæmia, 50

Fever, 368
Fibrin in blood, 48
Filariasis, 369
Filix mas poisoning, 221
Films of blood, how to make, 42
Films of marrow, how to make, 95
Finely granular leucocyte, 34
Follicular tonsillitis, 369
Fractures, 369
Frambœsia, 369

Gall bladder diseases, 369
Gall stones in cholæmia, 230
Gas poisoning, 263
Gastritis, 369
Gaucher splenomegaly, 131
    diagnosis, 131
    general pathology, 131
    general symptomatology, 131
    treatment, 132
Gelatin therapy, 340
General paralysis, 340
Gland puncture, 192
Glanders, 370
Glossitis in Addisonian anæmia, 247
Goitre, exophthalmic, 368
Gonorrhœa, 370
Gout, 370
Grain itch, 370

Hæmolymph glands, 29
Hæmolytic anæmia, 191
  jaundice, 221
Hæmophilia, 323
  age, 326
  arthritis, 326
  definition, 323
  diagnosis, 327
  etiology, 325
  general pathology, 323
  general symptomatology, 326
  treatment, 328
Hæmophilia neonatorum, 329
Hæmorrhage, serous, 331
  treatment of, 338
Hayems solution, 40
Heart disease, acquired, 177
    congenital, 177, 363
Heat exhaustion, 380
Herpes zoster, 370

Hodgkin's disease, 110
    age, 112
    alimentary system, 123
    blood, 115
    circulatory system, 114
    course, 125
    diagnosis, 126
    etiology, 112
    fever, 126
    general pathology, 110
    general symptomatology, 113
    liver, 123
    lymphatic system, 117
    marrow, 114
    nature, 110
    nervous system, 114
    onset, 113
    osseous system, 122
    remissions, 126
    respiratory system, 122
    sex, 112
    skin, 124
    special senses, 114
    spleen, 116
    treatment, 130
    urogenital system, 124
Hook-worm disease, 357
Hyaline cell, 37
Hydatid disease, 370
Hydroa æstivale, 265
Hydrophobia, 378
Hysteria, 371
Hæmatin, spectrum of, 284
Hæmatinuria, 267
Hæmatoporphyrin, extraction of, 266
    spectrum of, 284
    tests for, 266
Hæmatoporphyrinuria, 264
    course, 266
    definition, 264
    diagnosis, 266
    etiology, 264
    familial, 265
    general pathology, 264
    nature, 264
    onset, 265
    symptoms, 265
    urine, 266
Hæmochromatosis, 262
    age, 262
    course, 263
    definition, 262
    diagnosis, 264
    etiology, 262
    general pathology, 262
    general symptomatology, 263
    nature, 262
    onset, 262
    sex, 262
    skin, 263
    synonym, 262
Hæmochromogen, spectrum of, 284
Hæmoconia, 39
Hæmoglobin estimation, 42
    spectrum of, 284
Hæmoglobinuria, 265
    age, 271
    allied diseases, 268
    blood, 273
    circulatory system, 273
    course, 275
    definition, 267
    diagnosis, 275
    etiology, 270
    fever, 278
    general pathology, 267
    general symptomatology, 272
    icteric, 267
    lymph glands, 274
    nature, 267
    nervous system, 272
    onset, 272
    paroxysmal, 267
    sex, 271
    skin, 275
    spleen, 274
    synonyms, 267
    treatment, 275
    urogenital system, 274

Icteric hæmoglobinuria, 267
Idiopathic cyanosis, 292
    pernicious anæmia, 235
Increased red cell formation, 154
Infective hæmolytic anæmia, 235
    lymphocytosis, 304
    methæmoglobinæmia, 298

Infective methæmoglobinæmia, allied diseases, 300
  blood, 300
  course, 301
  definition, 298
  etiology, 300
  general pathology, 299
  general symptomatology, 300
  nature, 299
  synonyms, 298
  treatment, 301
Influenza, 371
Insanity, see under varieties
Insolation, 380
Intestinal obstruction, 371
Intravascular cyto-phagocytosis, 276
Iron therapy, 349

Jaundice, 371
  acholuric, 221
  hæmolytic, 221

Kahler's disease, 134

Large lymphocyte, 37
  mononuclear, 37
Lead poisoning, 371
Leprosy, 372
Leucocytes, the, 34
Leucocytosis, eosinophil, 303
  mixed, 305
  polymorph, 302
Leucopenia, 305
Leukæmia, chicken, 50
  experimental, 50
  hæmophilic tendency in, 59
  lymphatic, 51
  myeloid, 89
  splenic, 89
  spleno-medullary, 89
Leukanæmia, 333
Leukæmic retinitis, 57
Liver, the, 30
  acute yellow atrophy of, 356
  cirrhosis of, 362
Lymphadenoma, see Hodgkin's disease, 110
Lymphæmia, 51
  age, 53
Lymphæmia, albumosuria, 76
  alimentary system, 71
  associated syndromes, 82
  blood, 60
  circulatory system, 68
  clinical varieties, 82
  complications, 82
  course, 80
  definition, 51
  diagnosis, 81
  etiology, 53
  fever, 55
  general pathology, 52
  general symptomatology, 54
  glands other than lymphatic, 79
  liver, 74
  lymphatic system, 66
  marrow, 59
  metabolism, 80
  Miculikz' syndrome, 79
  nature, 51
  nervous system, 56
  onset, 53
  osseous system, 67
  pain, 56
  remissions, 81
  respiratory system, 69
  septic infection, 83
  sex, 53
  skin, 76
  special senses, 57
  spleen, 65
  synonyms, 51
  treatment, 85
  urogenital system, 75
Lymphatic Leukæmia, 51
Lymphatism, 148
  blood, 152
  definition, 148
  diagnosis, 152
  general pathology, 149
  general symptomatology, 150
  nature, 149
  synonyms, 148
  treatment, 152
Lymphocyte, large, 37
  small, 36
  Reider's, 38

Lymphocytosis, 304
  infective, 304
  in Hodgkin's disease, 116
Lymphocythæmia, 51
Lymphoid tissues, 28
Lymphoma, 134
Localised affections, 133
Lupus, 372

Malaria, 278, 372
Malignant endocarditis, 373
Malta fever, 373
Mania, 373
Marrow, the, 27
Mast cell, the, 36
Measles, 373
Megaloblast: *a large nucleated red cell*, 33
Megaloblastic anæmia, 235
Megalocyte: *a large red cell*, 34
Melancholia, 373
Meniere's syndrome in erythræmia, 159
    in myelæmia, 93
Meningitis, 367
Mesothorium, 108
Metachromatic staining, 38
Methæmoglobin, spectrum of, 284
Methæmoglobinæmia, infective, 298
Methæmoglobinuria, 267
  paroxysmal, 267
Microbic cyanosis, 298
Microblast: *a small nucleated red cell*, 34
Microcyte: *a small red cell*, 34
Migraine in erythræmia, 159
Miculikz' syndrome, 79
Miner's anæmia, 358
Mixed leucocytosis, 305
Moribund states, 373
Morphinomania, 374
Multiple Myeloma, 134
  blood, 136
  course, 137
  definition, 134
  diagnosis, 137
  lymph glands, 136
  marrow, 136
  onset, 135
Multiple Myeloma, pathology, 135
  spleen, 136
  symptoms, 135
  synonyms, 134
  treatment, 137
Mumps, 368
Mycosis fungoides, 374
Myelæmia, 89
  age, 92
  alimentary system, 101
  and cancer, 90
  ascites, 101
  benzol for, 108
  blood, 95
  chylous effusion, 100
  clinical varieties, 105
  combined sclerosis in, 93
  complications, 105
  congenital, 92
  course, 103
  definition, 89
  diagnosis, 106
  etiology, 92
  fever, 93
  general pathology, 91
  general symptomatology, 92
  intercurrent disease, 104
  jaundice, 102
  liver, 102
  lymph glands, 98
  marrow, 94
  muscles, 99
  nature, 89
  nervous system, 93
  onset, 92
  osseous system, 99
  remissions, 104
  respiratory system, 99
  sex, 92
  skin, 103
  special senses, 93
  spleen, 97
  splenectomy for, 107
  synonyms, 89
  thorium for, 108
  treatment, 107
  urogenital system, 103
Myelitis, acute, 375
Myelocytes, 37

Myelocythæmia, 89
Myeloid leukæmia, 89
Myelomatosis, 134
Myelopathic albumosuria, 134
  polycythæmia, 155
Myelophthisic anæmia, 191
Myocarditis, 375
Myxœdema, 375

Nephritis, 375
Neuritis, 375
Neutrophil leucocyte, 34
New growth, benign, 359
    malignant, 360
Normoblasts: *nucleated red cells of normal size*, 34
Normocyte: *the normal red cell*, 32
Nucleated red cells, 33

Obesity, 376
Origin of blood cells, 50
Osler's disease, 155
Osteomalacia, 376
Oxyhæmoglobin, spectrum of, 284

Pallor, significance of, 197
Pancreatitis, 376
Parasites, intestinal, 376
Parasitic anæmia, 191
Parasitic diseases of red cells, 278
Parotitis, 368
Paroxysmal hæmoglobinuria, 267
  methæmoglobinuria, 267
Pemphigus, 376
Pepys on transfusion, 343
Pericarditis, 376
Perisplenitis in myelæmia, 98
Peritonitis, 376
Pernicious anæmia, 235
Pertussis, 376
Phagocytic anæmia, 276
Phlebotomus fever, 377
Phosphorus, 180, 377
Pilocarpine, 180
Plague, 377
Platelets, 38
Pleurisy, 377
Pneumonia, 377
Poikilocytosis, 243

Polychromasia, 244
Polychromatophilia, 244
Polycythæmia, cryptogenetic, 155
  cyanotic, 155
  myelopathic, 155
  of congenital heart disease, 177
  of high altitudes, 176
  rubra, 155
  secondary, 175
  symptomatic, 175
  splenomegalic, 155
Polymorph, the, 34
Polymorph leucocytosis, 302
Polyuria in chlorosis, 311
Posthæmorrhagic anæmia, 191
Pre-myelocytes, 37
Primary epithelioma of spleen, 130
  splenomegaly, 137
Primitive cells, 26, 38
Pseudo-anæmia, 197
Pseudo-leukæmia, 110
  infantum, 214
Psoriasis, 378
Puberty, 378
Purpura, 331
  hæmorrhagica, 332
Pyæmia, 378

Rabies, 378
Raynaud's syndrome, 269
Rectal salines, 183
Recurrent pyrexia in Hodgkin's disease, 126
Red cells, the, 32
    enumeration, 42
    nucleated, 33
Relapsing fever, 378
Retinitis, leukæmic, 57
Rheumatism, acute, 379
Rickets, 379
Rieder's lymphocytes, 38

Salines, rectal, 183
Salvarsan, 348
Sand fly fever, 377
Sarcoma of adrenal, 69
Scarlet fever, 379
Scleroderma, 379
Scorbutus, 379

Scurvy, 379
Secondary anæmia, 191
    alimentary system, 208
    blood, 204
    circulatory system, 201
    definition, 195
    diagnosis, 212
    etiology, 195
    general pathology, 192
    general symptomatology, 197
    liver, 209
    lymph glands, 207
    marrow, 202
    nature, 191
    nervous system, 199
    respiratory system, 207
    skin, 211
    special senses, 201
    spleen, 207
    synonyms, 191
    treatment, 213
    urogenital system, 210
  polycythæmia, 175
Senile anæmia, 220
Septic anæmia, 191
Serous hæmorrhage, 331
Serum treatment, 338
Simple anæmia, 191
Small lymphocyte, 36
  mononuclear, 36
Snaefell mining disaster, 287
Spectra of blood derivatives, 284
Spleen, the, 29
  functions of the, 30
  primary epithelioma of, 130
Splenectomy, blood changes after, 380
  for cholæmia, 234
  for erythræmia, 172
  for myelæmia, 147
  for splenic anæmia, 146
Splenic anæmia, familial, 130
    of adults, age, 138
      alimentary system, 143
      allied diseases, 138
      blood, 141
      circulatory system, 140
      clinical varieties, 144
      complications, 145
      course, 144
Splenic anæmia of adults, definition, 137
      diagnosis, 145
      etiology, 138
      fever, 139
      general pathology, 138
      general symptomatology, 139
      liver, 143
      lymph glands, 142
      nature, 137
      nervous system, 140
      onset, 139
      remissions, 144
      respiratory system, 143
      sex, 138
      skin, 144
      spleen, 141
      special senses, 140
      synonyms, 137
      treatment, 146
      urogenital system, 144
    of infants, age, 215
      blood, 215
      course, 218
      complications, 219
      definition, 214
      diagnosis, 220
      etiology, 215
      fever, 215
      general pathology, 214
      general symptomatology, 215
      spleen, 217
      treatment, 219
  leukæmia, 89
Splenomedullary leukæmia, 89
Splenomegalic polycythæmia, 175
Splenomegalie primitive, 137
Splenomegaly of Gaucher, 130
  primary, 137
Starvation, 380
Status lymphaticus, 148
  thymicus, 148
Stippling, 222, 244
Sulph-hæmoglobin, spectrum of, 284
Sulph-hæmoglobinæmia, 292
  blood, 296
  definition, 292
  general pathology, 293
  general symptomatology, 294
  nature, 292

Sulph-hæmoglobinæmia, synonyms, 292
  treatment, 296
Sunstroke, 380
Surgical diagnosis, 334
Symmetrical glandular syndrome, 82
Symptomatic polycythæmia, 175
    blood, 181
    definition, 175
    etiology, 176
    general pathology, 175
    nature, 175
    symptoms, 180
    treatment, 181
Synovitis, 381
Syphilis, 381

Tabby-cat striation, 241
Tetanus, 381
Terminal leucocytosis, 374
Thoracic duct suppuration, 381
Thorium, 108
Thrombosis in chlorosis, 309
Thymectomy, 152
Thymic asthma, 148
Thymus, the, 26, 29
  death, 148
  tod, 148
Tinnitus, persistent, 93, 159
Transitional leucocyte, 36
Transfusion, 343
Traumatic anæmia, 191
Trichiniasis, 381
Tropho-neurotic anæmia, 191
Trypanosomiasis, 381
Tuberculosis, 382
Tuberculous chlorosis, 191
Typhoid fever, 382
Typhus fever, 382

Urohilin tests, 248
Urticaria in hæmoglobinuria, 275

Vaccination, 382
Vaccinia, 382
Vaquez' disease, 155
Varicella, 382
Variola, 382

White cells, the, 34
    enumeration of, 43

X-ray technique, 345
  treatment, 345
Xeroderma pigmentosum, 383

Yaws, 369
Yellow fever, 383

SAUNDERS' BOOKS

on

Nervous and Mental Diseases, Children, Hygiene, Nursing, and Medical Jurisprudence

W. B. SAUNDERS COMPANY

WEST WASHINGTON SQUARE PHILADELPHIA
9, HENRIETTA STREET COVENT GARDEN, LONDON

Dercum's Mental Diseases

Clinical Manual of Mental Diseases. By FRANCIS X. DERCUM, PH. D., M. D., Professor of Nervous and Mental Diseases at Jefferson Medical College, Philadelphia. Octavo of 425 pages. Cloth, $3.00 net.

TWO PRINTINGS IN FIVE MONTHS

This is a book *really useful to the family physician*—a book that tells you *definitely* how to diagnose, how to treat—either at home or in an institution—all classes of mental diseases. First, Dr. Dercum takes up the various primary forms of mental disease, giving emphasis to those you meet in your daily practice as general practitioner—delirium, confusion, stupor. Then melancholia, mania, the insanities of early life, paranoia, the neurasthenic-neuropathic disorders, and the dementias follow. The *mental disturbances of the infections* (syphilis, tuberculosis, malaria, pellagra, rheumatic fever, etc.), the various forms of intoxicational insanities, those due to metabolic disorders, visceral disease, diseases of the nervous system are all given you—and from *your* viewpoint. An important section is that devoted to the *insanities of pregnancy*. An entire part is devoted to the *psychologic interpretations of symptoms* as evolved by Freud and his disciples. You get a full discussion of the *rôle of dreams*.

The Medical World

"This book gives just the information necessary, and gives it in a style studiously adapted to the needs of the general physician."

Church and Peterson's Nervous and Mental Diseases

Nervous and Mental Diseases. By ARCHIBALD CHURCH, M.D., Professor of Nervous and Mental Diseases and Medical Jurisprudence, Northwestern University Medical School, Chicago; and FREDERICK PETERSON, M.D., President New York State Commission on Lunacy; Professor of Psychiatry at the College of Physicians and Surgeons, N.Y. Handsome octavo, 934 pages; 341 illustrations. Cloth, $5.00 net; Half Morocco, $6.50 net.

THE NEW (7th) EDITION

For this new seventh edition the entire work has been most thoroughly revised. To show with what thoroughness the authors have revised their work, we point out that in the nervous section alone over one hundred and fifty interpolations have been made, and, in addition, well over three hundred minor corrections. The chapters on Meningitis, Aphasia, Poliomyelitis, Pellagra, and Pituitary Diseases have been practically rewritten. A chapter on Oppenheim's Congenital Amyatonia has been introduced. The section on Mental Diseases has been wholly rearranged to conform to the latest classification, some obsolete matter struck out, and much new matter added. A number of chapters have been rewritten. This seventh edition embodies every substantial advance in the domains of nervous and mental diseases.

American Journal of the Medical Sciences

"This edition has been revised, new illustrations added, and some new matter, and really is two books. . . . The descriptions of disease are clear, directions as to treatment definite, and disputed matters and theories are omitted. Altogether it is a most useful text-book."

Kaplan's Serology of Nervous and Mental Diseases

Serology of Nervous and Mental Diseases. By D. M. KAPLAN, M.D., Director of Clinical and Research Laboratories, Neurological Institute, New York City. Octavo of 400 pages, illustrated.

JUST READY

This is an entirely new work, giving you the indications, contra-indications, preparation of patients, technic, after-phenomena, after-care, and disposal of the fluids obtained by lumbar puncture. You get a full discussion of the serology of all nervous and mental diseases of *non-luetic* etiology (including disorders of *internal secretion*), and of every type of *luetic* nervous and mental disease, giving the *Wassermann reaction in detail*, the use of *salvarsan* and *neosalvarsan*, etc.

Brill's Psychanalysis

THE PRACTICAL APPLICATION OF ALL FREUD'S THEORIES

Psychanalysis: Its Theories and Practical Application. By A. A. Brill, Ph. B., M. D., Clinical Assistant in Neurology at Columbia University Medical School. Octavo of 392 pages. Cloth, $3.00 net.

JUST OUT—NEW (2d) EDITION

To the general practitioner, who first sees these "borderline" cases (the neuroses and the psychoses), as well as to those specially interested in neurologic work, Dr. Brill's work will prove most valuable. Dr. Brill has had wide clinical experience, both in America and in Europe. The results of this experience you get in this book. Here you get the practical application of all Freud's theories—and from the pen of a man thoroughly competent to write.

Unlike other forms of psychotherapy, psychanalysis deals with the neuroses as *entities.* It does not treat them as symptoms, as do hypnotism, suggestion, and persuasion. Such treatment is similar to treating the cough or fever regardless of the causal disease. Psychanalysis concerns itself with the individual as a personality. It gives you a real insight into the neuroses and the psychoses.

Journal American Medical Association

"A splendid summary of Freud's writings. We believe this book to be the best one-volume exposition of the Freudian doctrine that has been written for the non-specialist."

Hunt's Diagnostic Symptoms of Nervous Diseases

Diagnostic Symptoms of Nervous Diseases. By Edward L. Hunt, M. D., Instructor in Neurology and Assistant Chief of Clinic, College of Physicians and Surgeons, New York. 12mo of 229 pages, illustrated. Cloth, $1.50 net.

JUST READY

Dr. Hunt gives you here those salient points and leading symptoms that will enable you to diagnose nervous and mental diseases. The book has chapters on examination, deformities, paralysis, tremors, trophic disorders, gaits, ataxia, convulsions, sensation, reflexes, eye symptoms, speech disturbances, aphasia, and electric reactions. The chapters on *gaits* takes up each gait in detail, giving you its characteristics and the diseases in which it occurs. Under *reflexes* the methods of eliciting the reflexes are clearly given and the diseases suggested by their absence stated. The value of *the eye in diagnosis* is brought out and the symptoms interpreted.

American Illustrated Dictionary

New (7th) Edition—5000 Sold in Two Months

The American Illustrated Medical Dictionary. A new and complete dictionary of the terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Veterinary Science, Nursing, and kindred branches; with over 100 new and elaborate tables and many handsome illustrations. By W. A. NEWMAN DORLAND, M. D. Large octavo, 1107 pages, bound in full flexible leather, $4.50 net; with thumb index, $5.00 net.

The American Illustrated Medical Dictionary defines hundreds of terms not defined in any other dictionary—bar none. It gives the capitalization and pronunciation of all words. It makes a feature of the derivation or etymology of the words. Every word has a separate paragraph, thus making it easy to find a word quickly. The tables of arteries, muscles, nerves, veins, etc., are of the greatest help in assembling anatomic facts. Every word is given its definition—a definition that *defines* in the fewest possible words.

Howard A. Kelly, M. D., *Johns Hopkins University, Baltimore.*

"The American Illustrated Dictionary is admirable. It is so well gotten up and of such convenient size. No errors have been found in my use of it."

Goodnow's First-Year Nursing

First-Year Nursing. By MINNIE GOODNOW, R. N., formerly Superintendent of the Women's Hospital, Denver. 12mo of 328 pages, illustrated. Cloth, $1.50 net.

Miss Goodnow's work deals *entirely* with the *practical* side of first-year nursing work. It is the *application* of text-book knowledge. It tells the nurse *how* to do those things she is called upon to do in her first year in the training school—the *actual ward work.*

Roberts' Bacteriology and Pathology for Nurses

Bacteriology and Pathology for Nurses. By JAY G. ROBERTS, PH. G., M. D., Oskaloosa, Iowa. 12mo of 206 pages, illustrated. Cloth, $1.25 net.

This new work is practical in the strictest sense. Written specially for nurses, it confines itself to information that the nurse should know. All unessential matter is excluded. The style is concise and to the point, yet clear and plain. The text is illustrated throughout.

Kerr's Diagnostics of Diseases of Children

Diagnostics of the Diseases of Children. By LEGRAND KERR, M. D., Professor of Diseases of Children, Brooklyn Postgraduate Medical School, Brooklyn. Octavo of 542 pages, fully illustrated. Cloth, $5.00 net; Half Morocco, $6.50 net.

FOR THE PRACTITIONER

Dr. Kerr's work differs from all others on the diagnosis of diseases of children in that the *objective symptoms* are particularly emphasized. The constant aim throughout has been to render a correct diagnosis as early in the course of the disease as possible, and for this reason differential diagnosis is presented from the very earliest symptoms. The many original illustrations will be found helpful.

New York State Journal of Medicine

"The illustrations are excellent and numerous. It will meet the needs of the great mass of physicians who treat the diseases of infancy and childhood."

Kerley's Pediatrics

Practice of Pediatrics. By CHARLES GILMORE KERLEY, M. D., Professor of Diseases of Children, New York Polyclinic Medical School and Hospital. Octavo of 878 pages, illustrated. Cloth, $6.00 net; Half Morocco, $7.50 net,

A NEW WORK—REPRINTED IN ONE MONTH

This is an entirely new work—not a revision of Dr. Kerley's earlier work. It is not a cut-and-dried treatise—but the *practice* of pediatrics, giving, of course, fullest attention to *diagnosis* and *treatment.* The chapters on the newborn and its diseases, the feeding and growth of the baby, the care of the mother's breasts, artificial feeding, milk modification and sterilization, diet for older children—from a monograph of 125 pages. Then are discussed in detail every disease of childhood, *telling just what measures should be instituted,* what drugs given, *60 valuable prescriptions* being included. The chapter on *vaccine therapy* is right down to the minnte, including every new method of proved value—with the exact technic. There is an excellent chapter on *Gymnastic Therapeutics,* giving explicit directions for the correction of certain abnormalities in which gymnastics have proved efficacious. Another feature consists of *the 165 illustrative cases—case teaching* of the most practical sort.

Sanders' Nursing

Modern Methods in Nursing. By GEORGIANA J. SANDERS, formerly Superintendent of Nurses at the Massachusetts General Hospital. 12mo of 881 pages, with 227 illustrations. Cloth, $2.50 net.

THE BEST YET

Miss Sanders' book gives only *modern* methods. Then it gives the *details* of nursing *operation cases*, both in the hospital and in the home. The thorough way in which *ward work* is taken up makes her book indispensable for teaching purposes. In giving directions for mustard baths, poultices, etc., the *quantities* are given exactly. This is an important point often overlooked.

Stoney's Nursing

Practical Points in Nursing. By EMILY A. M. STONEY. 12mo of 495 pages, illustrated. Cloth, $1.75 net.

THE NEW (4th) EDITION

In this volume the author explains the entire range of *private* nursing as distinguished from *hospital* nursing, and the nurse is instructed how best to meet the various emergencies of medical and surgical cases when distant from medical or surgical aid or when thrown on her own resources. An especially valuable feature will be found in the directions how to *improvise* everything ordinarily needed in the sick-room.

Stoney's Technic for Nurses

Bacteriology and Surgical Technic for Nurses. By EMILY A. M. STONEY, formerly Superintendent at Carney Hospital, South Boston. Revised by FREDERIC R. GRIFFITH, M. D., Surgeon, of New York. 12mo, 311 pages, illustrated. Cloth, $1.50 net.

THE NEW (3d) EDITION

Trained Nurse and Hospital Review

"These subjects are treated most accurately and up to date, without the superfluous reading which is so often employed. . . . Nurses will find this book of the greatest value both during their hospital course and in private practice."

Nursing in Diseases of the Eye, Ear, Nose, and Throat

Nursing in Diseases of the Eye, Ear, Nose, and Throat. By the Committee on Nurses of the Manhattan Eye, Ear, and Throat Hospital: J. EDWARD GILES, M. D., Surgeon in the Eye Department; ARTHUR B. DUEL, M. D. (Chairman), Surgeon in the Ear Department; HARMON SMITH, M. D., Surgeon in the Throat Department. Assisted by JOHN R. SHANNON, M. D., Assistant Surgeon in the Eye Department; and JOHN R. PAGE, M. D., Assistant Surgeon in the Ear Department. With chapters by HERBERT B. WILCOX, M. D., Attending Physician to the Hospital; and Miss EUGENIA D. AYERS, Superintendent of Nurses. 12mo of 260 pages, illustrated. Cloth, $1.50 net.

A VALUABLE BOOK

This is a practical book, prepared by surgeons who, from their experience in the operating amphitheater and at the bedside, have realized the shortcomings of present nursing books in regard to eye, ear, nose, and throat nursing. The scope of the work has been limited to what an intelligent nurse should know, and the style throughout is simple, plain, and definite.

New York Medical Journal

" Every side of the question has been fully taken into consideration."

Stoney's
Materia Medica for Nurses

Practical Materia Medica for Nurses, with an Appendix containing Poisons and their Antidotes, with Poison-Emergencies; Mineral Waters; Weights and Measures; Dose-List, and a Glossary of the Terms used in Materia Medica and Therapeutics. By EMILY A. M. STONEY, formerly of the Carney Hospital, South Boston. 12mo of 300 pages, Cloth, $1.50 net.

THE NEW (3d) EDITION

In making the revision for this new third edition, all the newer drugs have been introduced and fully discussed. The consideration of the drugs includes their sources and composition, their various preparations, physiologic actions, directions for administering, and the symptoms and treatment of poisoning.

Journal of the American Medical Association

" So far as we can see, it contains everything that a nurse ought to know in regard to drugs. As a reference-book for nurses it will without question be very useful."

Hoxie and Laptad's Medicine for Nurses **New (2d) Edition**

Medicine for Nurses and Housemothers. By GEORGE HOWARD HOXIE, M. D., Physician to the German Hospital, Kansas City, Mo.; and PEARL L. LAPTAD, formerly Principal of the Training School for Nurses, University of Kansas. 12mo of 351 pages, illustrated. Cloth, $1.50 net.

This work is truly a practice of medicine for the nurse, enabling her to recognize any signs and changes that may occur between visits of the physician, and, if necessary, to combat them until the physician's arrival. This information the author presents in a way most acceptable, particularly emphasizing the nurse's part.

Trained Nurse and Hospital Review
" This book has our unqualified approval."

McCombs' Diseases of Children for Nurses **New (2d) Edition**

Diseases of Children for Nurses. By ROBERT S. MCCOMBS, M. D., Instructor of Nurses at the Children's Hospital of Philadelphia. 12mo of 470 pages, illustrated. Cloth, $2.00 net.

Dr. McCombs' experience in lecturing to nurses has enabled him to emphasize *just those points that nurses most need to know.* The nursing side has been written by head nurses, especially praiseworthy being the work of Miss Jennie Manly.

National Hospital Record
" We have needed a good work on children's diseases adapted for nurses' use, and this volume admirably fills the want."

Wilson's Obstetric Nursing **The New (2d) Edition**

A Reference Hand-Book of Obstetric Nursing. By W. REYNOLDS WILSON, M. D., Visiting Physician to the Philadelphia Lying-in Charity. 32mo of 256 pages, illustrated. Flexible leather, $1.25 net.

Dr. Wilson's work discusses the subject of obstetrics entirely from the nurse's point of view, presenting in detail everything connected with pregnancy and labor and their management. The text is copiously illustrated.

American Journal of Obstetrics
" Every page emphasizes the nurse's relation to the case."

Frühwald and Westcott on Children

Diseases of Children. A Practical Reference Book for Students and Practitioners. By PROFESSOR DR. FERDINAND FRÜHWALD, of Vienna. Edited, with additions, by THOMPSON S. WESTCOTT, M. D., University of Pennsylvania. Octavo, 533 pages, 176 illustrations. Cloth, $4.50 net.

Boyd's State Registration for Nurses

State Registration for Nurses. By LOUIE CROFT BOYD, R. N., Graduate Colorado Training-school for Nurses. Octavo of 42 pages. 50 cents net.

Aikens' Primary Studies for Nurses

New (2d) Edition

Primary Studies for Nurses: A Text-Book for First-year Pupil Nurses. By Charlotte A. Aikens, formerly Director of Sibley Memorial Hospital, Washington, D. C. 12mo of 437 pages, illus. Cloth, $1.75 net.

This work brings together in concise form well-rounded courses of lessons in all subjects which, with practical nursing technic, constitute the primary studies in a nursing course.

Trained Nurse and Hospital Review

"It is safe to say that any pupil who has mastered even the major portion of this work would be one of the best prepared first-year pupils that ever stood for examination."

Aikens' Clinical Studies for Nurses

New (2d) Edition

Clinical Studies for Nurses. By Charlotte A. Aikens, formerly Director of Sibley Memorial Hospital, Washington, D. C. 12mo of 569 pages, illustrated. Cloth, $2.00 net.

This new work is written along the same lines as Miss Aikens' former work on "Primary Studies," to which it is a companion volume. It takes up all subjects taught during the second and third years and takes them up in a concise, forceful way.

Dietetic and Hygienic Gazette

"There is a large amount of practical information in this book which the experienced nurse, as well as the undergraduate, will consult with profit. The illustrations are numerous and well selected."

Aikens' Training-School Methods

Hospital Training-School Methods and the Head Nurse. By Charlotte A. Aikens, formerly Director of Sibley Memorial Hospital, Washington, D. C. 12mo of 267 pages. Cloth, $1.50 net.

Trained Nurse and Hospital Review

"There is not a chapter in the book that does not contain valuable suggestions."

Aikens' Hospital Management

Extremely Practical

Hospital Management. By Charlotte A. Aikens, formerly Director of Sibley Memorial Hospital, Washington, D. C. 12mo of 488 pages, illustrated. Cloth, $3.00 net.

The Medical Record

"Tells in concise form exactly what a hospital should do and how it should be run, from the scrubwoman up to its financing. A valuable addition to our literature on this subject."

Bolduan and Grund's Bacteriology for Nurses

APPLIED BACTERIOLOGY FOR NURSES. By CHARLES F. BOLDUAN, M. D., Assistant to the General Medical Officer; and MARIE GRUND, M. D., Bacteriologist, Research Laboratory, Department of Health, New York City. 12mo of 155 pages, illustrated. Cloth, $1.25 net.

We were fortunate in getting these practical physicians to write this work. It gives particular emphasis to the immediate *application* of bacteriology to nursing, only the really practical being included. A study of all the modes of infection transmission is presented. At the end of each chapter are suggestions for practical demonstration.

Register's Fever Nursing

A TEXT-BOOK ON PRACTICAL FEVER NURSING. By EDWARD C. REGISTER, M. D., Professor of the Practice of Medicine in the North Carolina Medical College. 12mo of 352 pages. Cloth, $2.50 net.

Hecker, Trumpp, and Abt on Children

ATLAS AND EPITOME OF DISEASES OF CHILDREN. By DR. R. HECKER and DR. J. TRUMPP, of Munich. Edited, with additions, by ISAAC A. ABT, M.D., Assistant Professor of Diseases of Children, Rush Medical College, Chicago. With 48 colored plates, 144 text-cuts, and 453 pages of text. Cloth, $5.00 net.

The many excellent lithographic plates represent cases seen in the authors' clinics, and have been selected with great care, keeping constantly in mind the practical needs of the general practitioner. These beautiful pictures are so true to nature that their study is equivalent to actual clinical observation. The editor, Dr. Isaac A. Abt, has added all new methods of treatment.

Lewis' Anatomy and Physiology **The New (3d) Edition**

ANATOMY AND PHYSIOLOGY FOR NURSES. By LEROY LEWIS, M. D., Formerly Surgeon to and Lecturer on Anatomy and Physiology for Nurses at the Lewis Hospital, Bay City, Michigan. 12mo of 344 pages, with 161 illustrations. Cloth, $1.75 net.

A demand for such a work as this, *treating the subjects from the nurses' point of view*, has long existed. Dr. Lewis has based the plan and scope of this work on the methods employed by him in teaching these branches, making the text unusually simple and clear.

The Nurses Journal of the Pacific Coast

"It is not in any sense rudimentary, but comprehensive in its treatment of the subjects in hand. The application of the knowledge of anatomy in the care of the patient is emphasized."

Friedenwald and Ruhräh's Dietetics **New (3d) Edition**

DIETETICS FOR NURSES. By JULIUS FRIEDENWALD, M. D., Professor of Diseases of the Stomach, and JOHN RUHRÄH, M. D., Professor of Diseases of Children, College of Physicians and Surgeons, Baltimore. 12mo volume of 431 pages. Cloth, $1.50 net.

This work has been prepared to meet the needs of the nurse, both in the training school and after graduation. It aims to give the essentials of dietetics, considering briefly the physiology of digestion and the various classes of foods and the part they play in nutrition.

American Journal of Nursing

"It is exactly the book for which nurses and others have long and vainly sought. A simple manual of dietetics, which does not turn into a cook-book at the end of the first or second chapter.

Paul's Fever Nursing

New (2d) Edition

NURSING IN THE ACUTE INFECTIOUS FEVERS. By GEORGE P. PAUL, M. D., formerly Assistant Visiting Physician to the Samaritan Hospital, Troy, N. Y. 12mo of 246 pages. Cloth, $1.00 net.

Dr. Paul has taken great pains in the presentation of the care and management of each fever. The book treats of fevers in general, then each fever is discussed individually, and the latter part of the book deals with practical procedures and valuable information.

The London Lancet

"The book is an excellent one and will be of value to those for whom it is intended. It is well arranged, the text is clear and full, and the illustrations are good."

Paul's Materia Medica for Nurses

New (2d) Edition

MATERIA MEDICA FOR NURSES. By GEORGE P. PAUL, M. D., formerly Assistant Visiting Physician to the Samaritan Hospital, Troy. 12mo of 282 pages. Cloth, $1.50 net.

Dr. Paul arranges the physiologic actions of the drugs according to the action of the drug and not the organ acted upon. An important section is that on pretoxic signs, giving the warnings of the full action or the beginning toxic effects of the drug, which, if heeded, may prevent many cases of drug poisoning.

The Medical Record, New York

"This volume will be of real help to nurses; the material is well selected and well arranged, and the book is as readable as it is useful."

Pyle's Personal Hygiene

The New (5th) Edition

A MANUAL OF PERSONAL HYGIENE: Proper Living upon a Physiologic Basis. By Eminent Specialists. Edited by WALTER L. PYLE, A. M., M.D., Assistant Surgeon to Wills Eye Hospital, Philadelphia. Octavo volume of 515 pages, fully illustrated. Cloth, $1.50 net.

The book has been thoroughly revised for this new edition, and a new chapter on Food Adulteration by *Dr. Harvey W. Wiley* added. There are important chapters on Domestic Hygiene and Home Gymnastics, Hydrotherapy, Mechanotherapy, and First Aid Measures.

Boston Medical and Surgical Journal

"The work has been excellently done, there is no undue repetition, and the writers have succeeded unusually well in presenting facts of practical significance based on sound knowledge."

Galbraith's Four Epochs of Woman's Life

Second Edition

THE FOUR EPOCHS OF WOMAN'S LIFE. By ANNA M. GALBRAITH, M.D. With an Introductory Note by JOHN H. MUSSER, M.D., University of Pennsylvania. 12mo of 247 pages. Cloth, $1.50 net.

Birmingham Medical Review

"We do not as a rule care for medical books written for the instruction of the public; but we must admit that the advice in Dr. Galbraith's work is in the main wise and wholesome."

Spratling on Epilepsy

EPILEPSY AND ITS TREATMENT. By WILLIAM P. SPRATLING, M. D., Professor of Physiology and Nervous Diseases, College of Physicians and Surgeons, Baltimore. Octavo of 522 pages, fully illustrated. Cloth, $4.00 net.

The Lancet, London

"Dr. Spratling's work is written throughout in a clear and readable style. . . . The work is a mine of information on the whole subject of epilepsy and its treatment."

Macfarlane's Gynecology for Nurses **New (2d) Edition**

A REFERENCE HAND-BOOK OF GYNECOLOGY FOR NURSES. By CATHARINE MACFARLANE, M. D., Gynecologist to the Woman's Hospital of Philadelphia. 16mo of 150 pages, with 70 illustrations. Flexible leather, $1.25 net.

A. M. Seabrook, M. D., *Woman's Medical College of Philadelphia.*

"It is a most admirable little book, covering in a concise but attractive way the subject from the nurse's standpoint."

Galbraith's Personal Hygiene for Women

PERSONAL HYGIENE AND PHYSICAL TRAINING FOR WOMEN. By ANNA M. GALBRAITH, M.D., Fellow New York Academy of Medicine, 12mo of 371 pages, with original illustrations. Cloth, $2.00 net.

Dietetic and Hygienic Gazette

"It contains just the sort of information which is very greatly needed by the weaker sex. Its illustrations are excellent."

De Lee's Obstetrics for Nurses **New (4th) Edition**

OBSTETRICS FOR NURSES. By JOSEPH B. DE LEE, M. D., Professor of Obstetrics in the Northwestern University Medical School. 12mo volume of 508 pages, fully illustrated. Cloth, $2.50 net.

J. Clifton Edgar, M. D.,

Professor of Obstetrics and Clinical Midwifery, Cornell Medical School, N. Y.

"It is far-and-away the best that has come to my notice, and I shall take great pleasure in recommending it to my nurses and students as well."

Davis' Obstetric Nursing **New (4th) Edition**

OBSTETRIC AND GYNECOLOGIC NURSING. By EDWARD P. DAVIS, A. M., M. D., Professor of Obstetrics, Jefferson Medical College and Philadelphia Polyclinic. 12mo of 480 pages, illustrated. Buckram, $1.75 net.

The Lancet, London

"Not only nurses, but even newly qualified medical men, would learn a great deal by a perusal of this book. It is written in a clear and pleasant style, and is a work we can recommend."

Beck's Hand-Book for Nurses **New (2d) Edition**

A REFERENCE HAND-BOOK FOR NURSES. By AMANDA K. BECK, of Chicago, Ill. 32mo of 200 pages. Flexible leather, $1.25 net.

Aikens' Home Nurse's Hand-Book

HOME NURSE'S HAND-BOOK. BY CHARLOTTE A. AIKENS. 12mo of 276 pages, illustrated. Cloth, $1.50 net.

The point about this work is this: It tells you and *shows* you just how to do those little but important things often omitted from other nursing books. "Home Treatments" and "Points to be Remembered"—terse, crisp reminders—stand out as particularly practical. Just the book for those who have the *home-care* of the sick.

Griffith's Care of the Baby

The Care of the Baby. By J. P. CROZER GRIFFITH, M. D., Clinical Professor of Diseases of Children, University of Penn.; Physician to the Children's Hospital, Phila. 12mo, 455 pp. Illustrated. Cloth, $1.50 net.

THE NEW (5th) EDITION

The author has endeavored to furnish a reliable guide for mothers. He has made his statements plain and easily understood, so that the volume will be of service to mothers and nurses.

New York Medical Journal

"We are confident if this little work could find its way into the hands of every trained nurse and of every mother, infant mortality would be lessened by at least fifty per cent."

Grulee's Infant Feeding

Infant Feeding. By CLIFFORD G. GRULEE, M. D., Assistant Professor of Pediatrics at Rush Medical College. Octavo of 316 pages, illustrated, including 8 in colors. Cloth, $3.00 net.

JUST ISSUED NEW (2d) EDITION

Dr. Grulee tells you *how* to feed the infant. He tells you—and *shows* by clear illustrations—the *technic* of giving the child the breast. Then artificial feeding is thoughtfully presented, including a number of simple formulas. The colored illustrations showing the actual shapes and appearances of stools are extremely valuable.

Ruhräh's Diseases of Children

A Manual of Diseases of Children. By JOHN RUHRÄH, M. D., Professor of Diseases of Children, College of Physicians and Surgeons, Baltimore. 12mo of 534 pages, fully illustrated. Flexible leather, $2.50 net.

THE NEW (3d) EDITION

In revising this work for the second edition Dr. Ruhräh has carefully incorporated all the latest knowledge on the subject. All the important facts are given concisely and explicitly, the therapeutics of infancy and childhood being outlined very carefully and clearly. There are also directions for dosage and prescribing, and many useful prescriptions are included.

American Journal of the Medical Sciences

"Treatment has been satisfactorily covered, being quite in accord with the best teaching, yet withal broadly general and free from stock prescriptions."

Keefer's Military Hygiene

Military Hygiene and Sanitation. By LIEUT.-COL. FRANK R. KEEFER, Professor of Military Hygiene, United States Military Academy, West Point. 12mo of 200 pages, illustrated.

JUST READY

This is a concise, though complete text-book on this subject, containing chapters on the care of troops, recruits and recruiting, personal hygiene, physical training, preventable diseases, clothing, equipment, water-supply, foods and their preparation, hygiene and sanitation of posts and barracks, the troopship, hygiene and sanitation of marches, camps, and battlefields, disposal of wastes, tropical and arctic service, venereal diseases, alcohol and other narcotics, and a glossary.

Bergey's Hygiene

The Principles of Hygiene: A Practical Manual for Students, Physicians, and Health Officers. By D. H. BERGEY, A. M., M. D., Assistant Professor of Bacteriology in the University of Pennsylvania. Octavo volume of 555 pages, illustrated. Cloth, $3.00 net.

FOURTH EDITION

This book is intended to meet the needs of students of medicine in the acquirement of a knowledge of those principles upon which modern hygienic practises are based, and to aid physicians and health officers in familiarizing themselves with the advances made in hygiene and sanitation in recent years. This fourth edition has been very carefully revised, and much new matter added, so as to include the most recent advancements.

Buffalo Medical Journal

"It will be found of value to the practitioner of medicine and the practical sanitarian; and students of architecture, who need to consider problems of heating, lighting, ventilation, water supply, and sewage disposal, may consult it with profit."

Fiske's Human Body

Structure and Functions of the Body. By ANNETTE FISKE, A.M., Graduate of the Waltham Training School for Nurses. 12mo of 221 pages, illustrated. **Cloth, $1.25 net.**

Bohm and Painter's Massage

Massage. By MAX BÖHM, M. D., of Berlin, Germany. Edited, with an Introduction, by CHARLES F. PAINTER, M, D., Professor of Orthopedic Surgery at Tufts College Medical School, Boston. Octavo of 91 pages, with 70 *practical* illustrations. Cloth, $1.75 net.

Draper's Legal Medicine

A Text-Book of Legal Medicine. By FRANK WINTHROP DRAPER, A. M., M. D., Late Professor of Legal Medicine in Harvard University, Boston. Octavo of 573 pages, illustrated. Cloth, $4.00 net; Half Morocco, $5.50 net.

Chapman's Medical Jurisprudence

Third Edition

Medical Jurisprudence, Insanity, and Toxicology. By HENRY C. CHAPMAN, M. D., late Professor of Institutes of Medicine and Medical Jurisprudence in Jefferson Medical College, Philadelphia. 12mo of 329 pages, illustrated. Cloth, $1.75 net.

Golebiewski and Bailey's Accident Diseases

Atlas and Epitome of Diseases Caused by Accidents. By DR. ED. GOLEBIEWSKI, of Berlin. Edited, with additions, by PEARCE BAILEY, M. D., Consulting Neurologist to St. Luke's Hospital, New York. With 71 colored illustrations on 40 plates, 143 text illustrations, and 549 pages of text. Cloth, $4.00 net. *In Saunders' Hand-Atlas Series.*

Hofmann and Peterson's Legal Medicine

In Saunders' Hand-Atlases

Atlas of Legal Medicine. By DR. E. VON HOFMANN, of Vienna. Edited by FREDERICK PETERSON, M. D., Professor of Psychiatry in the College of Physicians and Surgeons, New York. With 120 colored figures on 56 plates and 193 half-tone illustrations. Cloth, $3.50 net.

Jakob and Fisher's Nervous System

Saunders' Atlases

Atlas and Epitome of the Nervous System and its Diseases. By PROFESSOR DR. CHR. JAKOB, of Erlangen. Edited, with additions, by EDWARD D. FISHER, M. D., University and Bellevue Hospital Medical College. With 83 plates and copious text. Cloth, $3.50 net.

Crothers' Morphinism and Narcomania

Morphinism and Narcomania. By T. D. CROTHERS, M. D. 12mo of 351 pages. Cloth, $2.00 net.

Peterson and Haines' Legal Medicine and Toxicology

A thoroughly revised edition of this work is now in press. Every advance in these related subjects will be included, bringing the work right down to date.

American Pocket Dictionary **New (8th) Edition**

AMERICAN POCKET MEDICAL DICTIONARY. Edited by W. A. NEWMAN DORLAND, M. D., Editor "American Illustrated Medical Dictionary." Containing the pronunciation and definition of the principal words used in medicine and kindred sciences, with 64 extensive tables. With 677 pages. Flexible leather, with gold edges, $1.00 net; with patent thumb index, $1.25 net.

"I can recommend it to our students without reserve."—J. H. HOLLAND, M. D., *Dean of the Jefferson Medical College*, Philadelphia.

Morrow's Immediate Care of Injured **New (2d) Edition**

IMMEDIATE CARE OF THE INJURED. By ALBERT S. MORROW, M. D., Adjunct Professor of Surgery at the New York Polyclinic. Octavo of 360 pages, with 242 illustrations. Cloth, $2.50 net.

Dr. Morrow's book on emergency procedures is written in a definite and decisive style, the reader being told just what to do in every emergency. It is a practical book for every day use, and the large number of excellent illustrations can not but make the treatment to be pursued in any case clear and intelligible. Physicians and nurses will find it indispensible.

Powell's Diseases of Children **Third Edition, Revised**

ESSENTIALS OF THE DISEASES OF CHILDREN. By WILLIAM M. POWELL, M. D. Revised by ALFRED HAND, JR., A. B., M. D., Dispensary Physician and Pathologist to the Children's Hospital, Philadelphia. 12mo volume of 259 pages. Cloth, $1.00 net. *In Saunders' Question-Compend Series.*

Shaw on Nervous Diseases and Insanity **Fifth Edition**

ESSENTIALS OF NERVOUS DISEASES AND INSANITY: Their Symptoms and Treatment. A Manual for Students and Practitioners. By the late JOHN C. SHAW, M. D., Clinical Professor of Diseases of the Mind and Nervous System, Long Island College Hospital, New York. 12mo of 204 pages, illustrated. Cloth, $1.00 net. *In Saunders' Question-Compend Series.*

"Clearly and intelligently written; we have noted few inaccuracies and several suggestive points. Some affections unmentioned in many of the large text-books are noted." —*Boston Medical and Surgical Journal.*

Starr's Diets for Infants and Children

DIETS FOR INFANTS AND CHILDREN IN HEALTH AND IN DISEASE. By LOUIS STARR, M. D., Consulting Pediatrist to the Maternity Hospital, Philadelphia. 230 blanks (pocket-book size). Bound in flexible leather, $1.25 net.

Grafstrom's Mechano-Therapy **Second Revised Edition**

A TEXT-BOOK OF MECHANO-THERAPY (Massage and Medical Gymnastics). By AXEL V. GRAFSTROM, B. Sc., M. D., Attending Physician to the Gustavus Adolphus Orphange, Jamestown, New York. 12mo, 200 pages, illustrated. Cloth, $1.25 net.